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INSIDE

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SUMMER 2017

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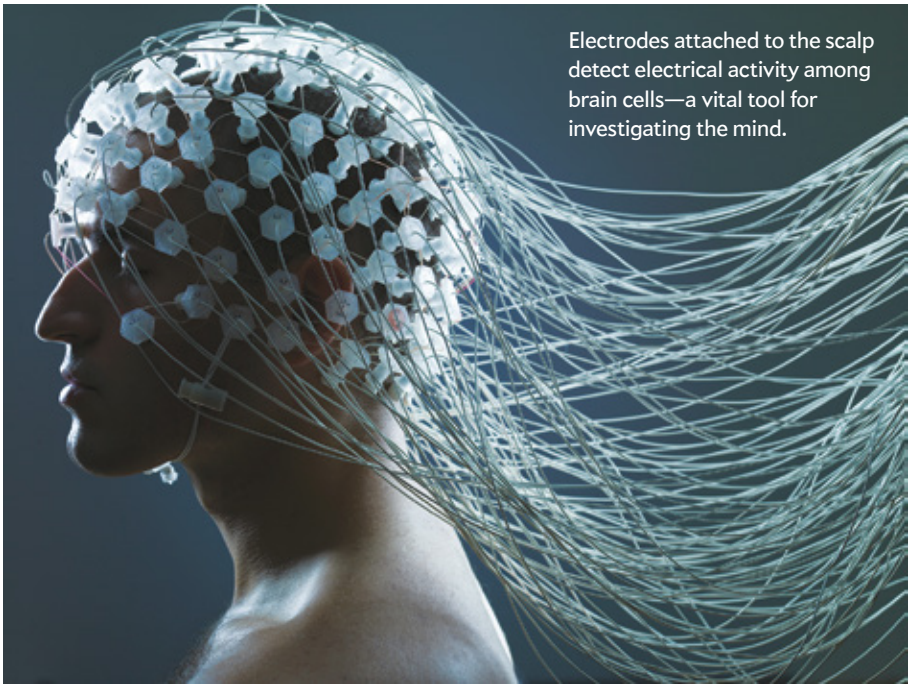

Electrodes attached to the scalp detect electrical activity among brain cells—a vital tool for investigating the mind.

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FROM THE EDITOR

Your Marvelous Mind

IN 2003 A PATIENT KNOWN AS TN LOST HIS SIGHT AFTER SUFFERING TWO SUCCESSIVE strokes; the visual cortex in his brain was damaged and his vision was totally gone, although the eyes themselves were still healthy. During one examination years after he lost his sight, researchers were flabbergasted to see TN carefully navigate a hallway full of overturned chairs, scattered boxes and other obstacles without colliding with a single thing. How was this possible for a person who was completely blind?

The human mind is capable of many remarkable feats. In this issue, scientists reveal what the latest research says about cognition and how we can improve our mental health. Plus, read up on some of the cutting-edge findings in neuroscience.

In the case of TN, his doctors and other researchers characterized his condition as "blindsight" and discovered that the brain can act on signals received by the retina even if the person is not aware of what he or she is seeing (*page 42*). Indeed, the mind perceives and processes information with or without our awareness. Readings from functional MRI scans show that the brain makes decisions even before we are aware we have made them (*page 24*). Consciousness can exist, but it can evade detection in vegetative patients. New research reveals that a small percentage of comatose patients are in fact fully aware (*page 106*).

How can we boost brain health? Three types of meditation help to achieve focus with less effort, reduce anxiety and improve sleep (*page 60*). An active social life and the Mediterranean diet are two of a handful of tactics that may help ward off Alzheimer's disease (*page 84*). Some brain-training programs could also prevent dementia (*page 76*). We all know there is nothing like a good night's sleep—sack time enhances mood, memory, immune function and hormonal balance—and yet the scientific underpinnings for sleep continue to be a mystery (*page 54*).

As Rafael Yuste and George M. Church note on page 92, a century of research on the brain has only inched us toward complete understanding of this most crucial human organ. New technologies using DNA and optogenetics are certainly pushing us closer, but the enigmatic human mind may remain biology's final frontier for years to come. SA

Andrea Gawrylewski
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MYSTERIES OF THE MIND

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CONSCIOUSNESS AS ART

Our subjective experience of the world may be like a visit to a gallery where the artist is our brain

By Nicholas Humphrey

Illustrations by Jon Han

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CONSCIOUSNESS MATTERS TO US. MANY WOULD SAY IT MATTERS more than anything. We relish the beauty of a winter sunset, the memory-fueled comforts of a homecoming, the inviting caress of a lover's hand. Conscious sensations lie at the core of our being. Without access to this marvel, we'd be poorer creatures living in a duller world. Yet the fundamental nature of consciousness remains a scientific mystery. The problem is not that we do not understand consciousness at all—some aspects of it are relatively easy to explain. The problem is that one aspect of it continues to baffle everyone, and that's the "feel" or "phenomenal character" of consciousness—or, as philosopher Thomas Nagel has put it, simply "what it is like." Biologist H. Allen Orr probably speaks for most scientists when, in a recent review of Nagel's book *Mind and Cosmos,* he writes: "I … share Nagel's sense of mystery here. Brains and neurons obviously have everything to do with consciousness, but how such mere objects can give rise to the eerily different phenomenon of subjective experience seems utterly incomprehensible."

Theorists tend to fall into one of two camps. Some assert that the manifestly eerie and ineffable qualities of subjective experience can only mean that these nonphysical qualities are inherent in the fabric of the universe. Others, including me, are more suspicious. They argue that consciousness may be more like a conjuring show, whereby the physical brain is tricking people into believing in qualities that don't really exist.

But no one wants to be told the latter story! So I am going to try telling the story in a different way. While I believe consciousness may indeed be a stage trick by the brain, I want to suggest that it is also a stroke of artistic genius. Consciousness as art is surely a more palatable notion than consciousness as illusion. I am not just looking to make friends for a theory that may be hard to swallow; I also want to influence the further questions scientists ask.

THE EXPERIENCE OF PAIN

SUPPOSE YOU prick your thumb. Your brain responds to signals from the thumb with an internalized hurt response, the neural correlate of pain. From an objective point of view, this response is nothing more than the activity of nerve cells. From your subjective point of view, however, this experience seems to be nothing less than—well—conscious pain.

IN BRIEF

Debate rages as to whether the qualities of conscious experience can be explained simply as the workings of the physical brain or whether there must be some kind of additional ingredient that lies beyond the scope of physics.
Considering consciousness to be an illusion—a mere trick of the physical brain—offends people, so perhaps we should think of consciousness as art instead. Whereas people resent being duped by illusions, they are proud to be art lovers.
If the human brain has evolved to create masterpieces of consciousness for our private enjoyment, scientists will want to know what the evolutionary payoff is. Perhaps the purpose of this brain art is to make people fall in love with themselves—and other people, too.

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SUBJECTIVE QUALITY of consciousness seems to defy explanation. Why does the sound of a trumpet or the pain of a bee sting feel to you the way it does?

Yet how can this transformation possibly occur? How can there be physical matter on one side of the equation and nonphysical consciousness on the other? Philosophers talk about the existence of an "explanatory gap" here. As Colin McGinn has put it, "You might as well assert that numbers emerge from biscuits or ethics from rhubarb."

I am a scientist. But when the philosophical skeptics put it like that, I agree they may be right. You really can't get numbers from biscuits, and you really can't get pain from nerve cells, at any rate not if the pain is conceived of as some kind of alchemical substance exuded by the brain.

But what if this is simply the wrong way to conceive of pain? What if pain is nothing other than your "inner picture" of the neural activity? And what if this picture is actually pure make-believe—part of your brain's internal conjuring show?

These are some big what-ifs, and we should tread carefully. I may be convinced that some such explanation must be true, but other theorists treat the idea with incredulity and even scorn. In her book *Are You an Illusion?* British philosopher Mary Midgley's answer is to pinch herself, feel the reality of the sensation and say, in effect, "Don't be daft."

Midgley balks at the suggestion that she is an illusion because she takes it to imply she is some kind of mistake. But let's try telling the story in another way. How about suggesting that when you see red or taste a lemon, your brain is creating something like a cubist painting—not necessarily a misrepresentation but an artistic *re*-presentation of the facts? Would Midgley feel better if she could be persuaded that she is actually a remarkable work of art?

CONSCIOUSNESS, DEFINED

LET'S STEP BACK so we can place this new idea in the context of consciousness in general. The "eerily different phenomenon" to which Orr drew attention may still prove to be the sticking point. But we should not assume at the start that everything about consciousness is impossibly difficult. Indeed, the first steps toward a scientific understanding are straightforward and have already been taken.

We should begin with a definition. Although opinions differ, I think it is helpful to start by describing consciousness simply as introspective access to mental states. That is to say, you, the subject of consciousness, are conscious of mental states—perceptions, memories, wishes, and so on—just insofar as you know about them by looking in on your own mind.

Note that we encounter only one you here. When you feel pain, or you want breakfast, or you remember your mother's face, it's the same you in each case. This unity is not a logical necessity. It is theoretically possible your brain could have housed several independent versions of you, each representing a different module of the mind. Indeed, you may actually have started out this way at birth. As your life got going and your body began interacting with the world, however, the separate subjects soon became orchestrated as one. Your perceiving self, your remembering self, your acting self became merged into the one big you.

The unity of the self underlies the most obvious function of consciousness: namely to provide a mind-wide forum for planning and decision making. Your brain has brought information from different modules to the same table, as it were, to allow fertile cross talk. This integration opens the way for a central pro-

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cessing unit to recognize patterns, marry past and future, assign priorities, and so on. Computer programmers might call this central processor an "expert system," rather like an intelligent autopilot. You call the onboard pilot "I."

With all this activity happening on a single stage, consciousness has become something like a theater, where the engine of the mind is on show. You find you can reflect on what's going on. And this capacity for self-reflection supports a second important function of consciousness: to allow you to appreciate how your mind works. Observing, for example, how beliefs and desires generate wishes that lead to actions, you find your mind revealed as having a clear psychological structure. You begin to gain insight into why you think and act the way you do: you can explain yourself to yourself and explain yourself to other people, too. What's more, you have a model for explaining other people to yourself. Consciousness has laid the ground for what psychologists call "theory of mind."

So far so good. We have a definition, two important functions for consciousness and a suggestive metaphor, the theater of consciousness. We have not yet had to raise the question of illusion, and—for that reason perhaps—nothing about this account of consciousness seems completely incomprehensible. In fact, neuroscientists are already making considerable headway in discovering how the brain could realize some of these features. Stanislas Dehaene of the Collège de France in Paris has been mapping what he calls "the global neuronal workspace." Giulio Tononi of the University of Wisconsin–Madison has proposed a statistical model of "integrated information." Christof Koch of the Allen Institute for Brain Science in Seattle (who serves on *Scientific American*'s board of advisers) has identified a brain structure, the claustrum, as a likely candidate for the master of ceremonies.

EERINESS OF CONSCIOUSNESS changes your sense of who and what you are. It feeds your self-worth, your joy in life, your fear of death. Perhaps the evolutionary function of "consciousness as art" is to make you fall in love with the artist—yourself.

THE EERIE QUALITY

HOLD ON, HOWEVER. The picture that is emerging may not be incomprehensible but neither is it eerie. Where's the peculiar what-it-is-like-ness that Nagel pointed to? Where's the phenomenal quality philosophers beef about?

We should note that the quality in question does not pervade every aspect of consciousness. In fact (although not everyone agrees), I'd say this quality is not a feature of higher levels of cognition. There is no "what it is like" for you to have the thought that two plus two is four. Rather this quality seems to kick in only at a more animal level, in the way you represent what's happening at your bodily sense organs. Of the variety of mental states of which you're conscious, it is your sensations—and only your sensations—that have this peculiar dimension to them.

The special qualities of sensations are what philosophers call "qualia." Although scientists don't often use that term, there's no denying that qualia present natural science with a spectacular challenge. Koch wrote to me not long ago that "it is bizarre that brain matter should exude these phenomenal feelings. Consciousness is so vivid, and its properties appear so otherworldly, that it seems to call for God." He may have been half-joking. But who's laughing? Short of invoking some supernatural agency, where are we to go?

Most theorists now accept that only two options can be taken seriously, along the dividing line I sketched earlier. We can be realists about qualia, or else we have to be illusionists. Unfortunately, both options come at a considerable price.

Realists take qualia at face value. In their view, if your sensations appear to have qualities that lie beyond the scope of physics, then they really do have such qualities. And these realists explain

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their reasoning by suggesting that the brain activity underlying sensations already has consciousness latent in it as an additional property of matter—a property as yet unrecognized by physics but one that you, the conscious subject, are somehow able to tap into. The price for this explanation is that it implies that the standard physical description of the world is radically incomplete.

Illusionists take the contrary line. If your sensations appear to have these qualities, then your physical brain is playing tricks on you. Your brain can pull off such magical effects because it houses a computational engine that deals in symbols, and physically based symbols can perfectly well represent states of affairs that do not and could not exist. The price for this explanation is that it devalues not only the mystery but the majesty of the core experience.

ART RATHER THAN ILLUSION

I BELONG, AS I SAID, to the illusionist camp, and I've provided extensive psychological and evolutionary arguments for my position over the years. But even if illusionism is scientifically correct, I well understand why it is not the story many people want to hear. So now let me try sweetening the pill. Why might it be more persuasive if we were to talk about qualia as art rather than illusion? I am not proposing an alternative theory to illusionism, but my hope is that shifting the emphasis in a positive direction may in fact make the illusionist theory more scientifically acute and at the same time more humanly agreeable.

First, we generally consider illusions to be sources of error, but we think of works of art as sources of enlightenment. In Pablo Picasso's words, "Art is a lie that makes us realize truth." Or in Paul Klee's, "Art does not reproduce the visible; rather it makes visible." Or in Friedrich Nietzsche's, "Art is not merely imitation of the reality of nature but rather a metaphysical supplement to the reality of nature." Ellen Dissanayake, a writer on art and evolution, has characterized art in general as the activity of "making special." By likening sensations to works of art, therefore, we can emphasize how ordinary information from the sense organs is transformed and embellished on the way to consciousness.

Next, we tend to think of illusions as fortuitous or accidental, but we think of works of art as necessarily involving an artist. So now we can draw attention to the active agency behind conscious sensations. The immediate agent—if not the ultimate designer—is your own brain, when it responds to sensory information by creating the neural correlates of qualia. Neuroscientists do not yet know what these neural correlates amount to (although I have made some detailed suggestions in my book *Soul Dust*). Could it be your brain employs some of the same aesthetic principles that artists use?

Furthermore, as Marcel Duchamp said, "The artist performs only one part of the creative process. The onlooker completes it, and it is the onlooker who has the last word." Art necessarily implicates an audience. So now we can also draw attention to your self as the reactive and appreciative observer of the brain art. Moreover, drawing on what we know about art appreciation, we can go on to ask how you evaluate qualia, cognitively and emotionally. Are there individual differences in susceptibility to the illusory message? Do people learn to read qualia, as they learn to appreciate art? What does it take to become a qualia connoisseur?

Last and most important, we seldom regard illusions as having any human value, but we expect works of art to be intellectually and spiritually nourishing, good for our souls. We don't care to be dupes of an illusion, but we are proud to be art lovers. Thus, this way of thinking about sensations allows us to look out for—and celebrate—the psychological growth that human beings derive from participating in the self-made show.

THE BEAUTY OF CONSCIOUSNESS

THE CHIEF SCIENTIFIC BONUS of conceptualizing consciousness as art may prove to be precisely this: that it raises new questions for an evolutionist about the value and purpose of consciousness. If sensations are art, the artist behind them is actually not the individual brain as such. Rather the artist—the ultimate designer—must be the evolutionary forces of natural selection, which have contrived to put in place the genetic code for building the qualia-generating brain. Yet natural selection promotes only variants that contribute to biological survival. What then can be the biological advantage of a brain that delivers such awe-inspiring but seemingly superfluous flummery?

The analogy with art continues to help. Charles Darwin struggled to explain several of the more exotic features of animal courtship until he hit on the idea that such displays are designed not to serve any obvious utilitarian purpose but rather to show off—and to seduce. The peacock's gaudy tail does not enable him to fly any higher, but it raises his status in the eyes of the peahen. Darwin suggested that one of the chief functions of human art, too, is to induce the onlooker to fall in love with the artist.

Thus, an extraordinary possibility suggests itself: the evolutionary function of brain art is nothing less than to induce you to fall in love with yourself. The qualia of visual sensation, for example, are not necessary to your perception of the outside world, but—along with all your other sensations—they enlarge your sense of who you are. Qualia feed your self-worth, your joy in life, your fear of death. Nor is this idle speculation. In my book *Seeing Red,* I describe a remarkable case of a woman with a form of "blindsight"—vision without conscious qualia—whose sense of self seemed to be so damaged that she became suicidal.

French philosopher René Descartes famously intoned: "I think, therefore I am." But the self that evolves around sensory consciousness is deeper and more generous: I feel, therefore I am. Therefore you feel, and you are, too. Consciousness, by placing you at the center of this brilliant and perplexing work of art, encourages you to think of all humans as equally touched by magic. Thus, you end up, though by a different route, just where Midgley, Nagel and others want you to be: as centers of spiritual excellence, spreading the joy. SA

Nicholas Humphrey is emeritus professor of psychology at the London School of Economics and a professor at Darwin College, Cambridge. He won the 2015 Mind & Brain Prize.

MORE TO EXPLORE

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The Magic of Consciousness. Royal Institution video, with Nicholas Humphrey: www.youtube.com/watch?v=NHXCi6yZ-eA

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THE ENGINE OF MEMORY

Even after his death, the famous amnesic H.M. is revolutionizing our understanding of how memory works and how we maintain it as we age

By Donald G. MacKay

I REMEMBER MEETING H.M. IN THE SPRING OF 1967, WHEN HE WAS perhaps 40 years old and I was 16 years his junior. My mentor, Hans-Lucas Teuber, brought him to my tiny office across from the psychology department library at the Massachusetts Institute of Technology. I recall H.M.'s thin, smiling, rather handsome face as he squeezed into the doorway with Teuber, who introduced us as "Don" and "Henry," as if we might become buddies. I think I called Henry "sir" as we shook hands because he was already a minor M.I.T. celebrity. Teuber assured Henry that he would enjoy taking part in my experiment on sentence comprehension, something he was good at, and excused himself.

Illustration by Eiko Ojala

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AT AGE 27, HENRY MOLAISON, known to the public as H.M. until his death in 2008, underwent surgery that removed the brain's engines of memory formation. As a result, he could no longer remember new experiences in a normal way. As he aged, his established memories degraded abnormally as well, a mystery that an evolving body of work has begun to solve. *Clockwise from left:* H.M. appears as a high school senior, in his early 30s, at about age 50, at age 60, and as an old man.

As we climbed the stairs to the testing room, it never crossed my mind that this quiet man would become a major focus of my research during the next half a century. I unlocked the door and seated Henry at a wooden desk facing mine, sunlight streaming into the room from large windows to my right. In front of me I had two stopwatches and a stack of 32 short sentences typed onto three-by-five index cards. I started a tape recorder and began what I thought would be a fairly routine experiment.

Since 1967 Henry's initials have become the most famous in the history of the brain sciences. (The public only learned his full name, Henry Molaison, after his death in 2008.) Henry's rise to fame began about 13 years earlier at age 27, when a neurosurgeon removed a small portion of his midbrain known as the hippocampal region. This removal largely cured Henry's life-threatening epilepsy but had an unintended side effect: for the remainder of his life, Henry could no longer learn new information in a normal manner, a condition that revolutionized the study of memory and the brain.

Studying Henry helped others before me to clarify the role of the hippocampal region in forming complex memories for novel, personally experienced events. My research with Henry showed that the hippocampal region also helps us to retain established memories, by essentially forming damaged memories anew. Without such renovation, we would forget forever.

This idea sweeps away the notion of memory degradation as a passive, inexorable process. The mechanism by which we revive old memories appears to offset some of the recollection difficulties that occur during normal aging. Rather than allowing the pieces of our past to simply drift away with time, the brain stays actively involved in restoring damaged memories. These insights also solve a 100-year-old mystery in psychological research on amnesia. Until now, no one clearly understood why people with amnesia, who by definition have difficulty learning information encountered after their brain damage, usually have problems remembering information they learned many years before that damage.

"WHO ARE YOU?"

IN THE 1987 FILM *Overboard,* a socialite played by Goldie Hawn bumps her head falling from her yacht and suffers memory loss so complete that it destroys her identity. Movie plots invoking amnesia often feature dramatic scenes in which trauma immediately wipes out a character's past, but the protagonist can still form memories of new facts and experiences. Such cases are pure

IN BRIEF

People with amnesia have difficulty learning new information but (except for those who have Alzheimer's disease) never lose everything they have learned in the past.

Synaptic connections in the neocortex deteriorate with age, so that memories stored there become increasingly weak and fragmented. The memories that suffer the most are those we use infrequently.

The latest data on the famous amnesic H.M. suggest that one important role of the hippocampus is to craft new memories to replace those that have become degraded over the years.

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fiction. Real amnesic individuals have difficulty learning new information but (except for cases of Alzheimer's disease) never lose all of their past, whether caused by a brain lesion, a concussion, alcohol poisoning or a viral infection.

Henry became amnesic in 1953 after his operation, which removed the brain's central engines for memory formation. His ability to remember new experiences became severely impaired. Brief interruptions wiped out his extremely fragile memories for recent events (his episodic memories). If a knock at the door during your experiment called you away for even a minute, when you returned Henry might ask, "Who are you?" You needed then to reintroduce yourself and once again describe the task you wanted him to continue.

Henry could not make mental impressions of ephemeral experiences stick. In documenting such memory deficits, my mentor and others established the critical role of the hippocampal region in forming new long-term memories. Yet Henry's recollection of events and facts learned before his lesion seemed perfectly normal, at first. He pronounced everyday words fluently, easily asked questions such as "Have we met before?" and lucidly answered questions about where he went to high school and where he was born.

In the 1960s psychologist Wayne Wickelgren, then at M.I.T., proposed that the hippocampal region facilitates the creation of permanent memories in the brain's exterior rind, the neocortex. These cortical memories take the form of strengthened connections among neurons. The neocortex thus resembles the repository, and the hippocampus acts like a builder of memories, whether these are episodic, such as my memory of meeting Henry, or factual (semantic), such as the meaning of a word. This idea, which emerged in large part from work with Henry, was a dramatic revision of earlier thinking. Previously researchers had conceived of the hippocampal region as a direct storehouse of memories. Because Henry's neocortex was unimpaired, it therefore made sense that his word memories, stored before his operation, would be intact.

IN THIS POSTMORTEM PHOTOGRAPH of the brain of the amnesic H.M., white lines highlight the regions of the medial temporal lobes where a surgeon suctioned out part of his hippocampus, a brain region that governs long-term memory storage.

So the day I met Henry, I assumed he would perform well on my sentence comprehension test. I instructed Henry to read 32 ambiguous sentences. For example, the sentence "I just don't feel like pleasing salesmen" could mean either "I don't want to please salesmen" or "I don't want agreeable salesmen around." Henry's task was to find and describe both meanings for each sentence as quickly as possible.

Henry discovered both meanings for just 20 percent of the sentences, whereas Harvard University students had no trouble identifying any of the ambiguities. Henry also took 10 times as long as the college students had—more than 49 seconds, on average—to begin his descriptions. And Henry's descriptions tended to be incomplete, inaccurate and difficult to understand. For example, at one point Henry explained the two meanings of "I just don't feel like pleasing salesmen" as follows: "The person doesn't like salesmen that are pleasing to him. Uh, and that personally he doesn't like them, and and [sic] personally he doesn't like them [sic], and then I think of a phrase that he would say himself, he doesn't, uh, pleasing, as conglamo [sic], of all of pleasing salesmen."

At the time, I did not know what to make of these observations. A confusing array of questions came to mind that I only later categorized and addressed. Why did Henry have difficulties understanding my sentences? Neurologists since 1874 had believed that a region of the cortex now known as Wernicke's area carries out sentence comprehension. Yet Henry's neocortex was undamaged. His incoherence also baffled me because Broca's area, in another part of the neocortex, was thought to be the engine that created grammatical sentences. And what did Henry mean by "conglamo"—a conglomeration? A concatenation? Or a fusion of both words?

At age 40, Henry seemed too young to be experiencing word-finding difficulties, but something was clearly happening to his lexical memories. I just had no idea what that was. Only later would I discover a connection between Henry's damaged hippocampal region and his memory for words he had learned in adolescence.

FROM "POSTMORTEM EXAMINATION OF PATIENT H.M.'S BRAIN BASED ON HISTOLOGICAL SECTIONING AND DIGITAL 3D RECONSTRUCTION," BY JACOPO ANNESE ET AL., IN *NATURE COMMUNICATIONS*, VOL. 5; JANUARY 2014

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A TYPE OF FASTENER MADE OF NYLON

AFTER EARNING MY PH.D. from M.I.T. in 1967, I became a professor at the University of California, Los Angeles. For me, language proved to be a useful way to study many aspects of memory, including the impact of aging on our ability to remember familiar words. Unlike memories for personal experiences, which vary from person to person, we all learn the same spelling, meaning and pronunciation for words. The uniformity of word knowledge in young adults made it easy for me to determine whether aging was responsible for the deteriorating word memories of older adults.

My research during subsequent years delineated specific age-related changes in how we remember words. In 1990, for example, my colleagues and I reported that as we age, the ability to recall pronunciations of familiar but rarely used words declines systematically. When we gave people a definition such as "a type of interlocking fastener made of nylon," adults aged 65 and older could not bring to mind the word "Velcro" as often or as readily as adults 18 to 20 years old. For the older adults, the word more often remained on the tip of their tongue: they knew the meaning of the word, often its first speech sound (V) and its number of syllables but could not retrieve the entire word.

AT AGE 40, HENRY SEEMED TOO YOUNG TO BE EXPERIENCING WORD-FINDING DIFFICULTIES, BUT SOMETHING WAS CLEARLY HAPPENING TO HIS LEXICAL MEMORIES.

In 1998 my team published a related discovery: the ability to spell familiar but irregularly written words such as "rhythm," "physicist" and "yacht" also declines with aging. Adults 60 years or older in our experiments produced reliably more misspellings than young adults. Even though the older adults realized that they once spelled "bicycle" without difficulty, they could no longer remember whether it was spelled "bicycle," "bysicle" or "bisykle" until they reencountered "bicycle" in print.

Our discoveries indicated that normal adults older than 65 experience slight but reliable difficulties in retrieving lexical information learned decades earlier, difficulties that become progressively more severe with aging. At first, the information would come to mind after a delay, but as the memory grew more fragile over time, it often became irretrievable. At the extreme, even seeing the word failed to bring to mind its correct pronunciation, spelling and meaning. (To learn what aspects of memory decline with age and what to do about it, see the box on page 16.)

Tip-of-the-tongue and tip-of-the-pen experiences are thought to arise when the relevant neural connections in the neocortex degrade. The representations of our knowledge of how to spell "rhythm" or pronounce "Velcro" weaken with time if these words are rarely spoken, seen or heard. Frequent use or recent exposure to a word strengthens those connections and prevents forgetting. Older people show no deficits in understanding, spelling or recalling words they often use, hear or write.

AN AGING AMNESIC

AS I INVESTIGATED THE EFFECTS of normal aging on word memories, I returned to my 1967 questions about Henry's lexical memories. I reexamined a 178-page transcript of interviews with Henry recorded in 1970 by William Marslen-Wilson, then a fellow graduate student at M.I.T. The recording revealed that at age 44, Henry experienced unusual difficulties retrieving rarely used words. Instead of describing people as "more relaxed," Henry said they were "more eased." Similarly, he referred to a model airplane as made of "bamboo" or "like wood" rather than "balsa." These errors haunted me, as I had never seen such lapses in someone so young. It was as if Henry's lexical memories were undergoing premature deterioration.

Then an idea came to me. Perhaps Henry's word-finding problems reflected an inability to relearn information he had completely forgotten. After all, his fundamental deficit was an inability to represent new information in his cortex. I reasoned that Henry's hippocampal damage may have prevented him from offsetting the degradation that accompanies normal aging. This inability could have transformed the usually minor word-retrieval problems of older adults into major impairments.

But so far I only had hints that Henry suffered such severe memory gaps. To determine whether Henry's memories were in fact fading abnormally, I needed to compare his word knowledge in his early 70s with that of people with normal memory who resembled Henry in all other respects. I also needed to document how Henry's lexical memories changed during his lifetime. Evidence of unusual memory degradation might for the first time explain why most individuals suffering damage to the hippocampal region end up forgetting information learned before their lesion.

When Henry was 71 and 73 years old, I asked my postdoctoral fellow, Lori E. James, now a psychologist at the University of Colorado Colorado Springs, to fly to Boston to test Henry's lexical memory at M.I.T. I wanted to assess Henry's ability to define words, with questions such as "What does 'squander' mean?" and to see whether he could tell which words—"squander," say—are real and meaningful rather than invented. I also wished to evaluate how well Henry could retrieve the sounds of words for the purpose of naming familiar objects in pictures and reading rarely used words aloud. Finally, I was curious whether Henry could recall irregular spellings of words such as "rhythm."

James and I created sets of words that Henry had almost certainly used earlier in his life, based on the age at which each word is normally acquired and the extensive Marslen-Wilson transcript of words Henry had used in conversation at age 44. We categorized our words as high frequency or low frequency based on available statistics on how often people use them. (I discuss only our results for low-frequency words because Henry's performance for common words was unremarkable.)

Testing Henry was the easy part. I, along with my wife, Deborah M. Burke, a psychologist at Pomona College, and our colleagues then spent many years finding healthy individuals aged 71 or 73 years with normal memory whose education, intelligence, occupation and socioeconomic background were similar to Henry's. We culled our candidates from the records of more than 750 older adults in the participant pools of the U.C.L.A. Cognition and Aging Laboratory, the Claremont Project on Memory and Aging, and retirees from clerical or physical plant positions at the Claremont Colleges.

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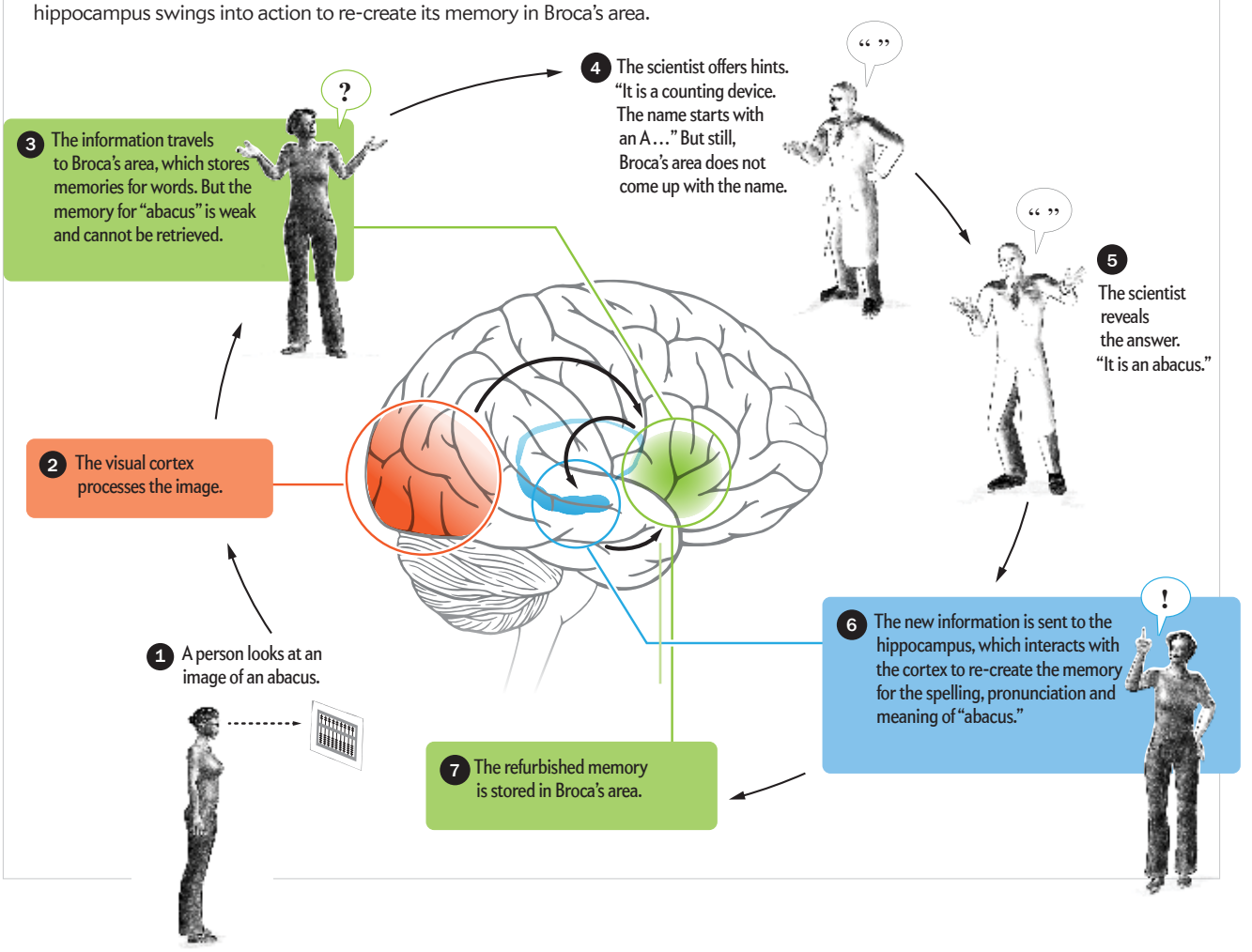
How to Restore a Memory

Our memories gradually degrade over time if we do not use them. The hippocampus, which governs memory formation, is now thought to engineer the restoration of fading memories in response to experience. For example, if someone has not recently encountered the name of an object such as an abacus, that individual may not be able to recall that name—which had been stored in Broca's area, a region that houses names and labels—when she sees a picture of an abacus. But when she is told the name, the hippocampus swings into action to re-create its memory in Broca's area.


1 A person looks at an image of an abacus.
2 The visual cortex processes the image.
3 The information travels to Broca's area, which stores memories for words. But the memory for "abacus" is weak and cannot be retrieved.
4 The scientist offers hints. "It is a counting device. The name starts with an A…" But still, Broca's area does not come up with the name.
5 The scientist reveals the answer. "It is an abacus."
6 The new information is sent to the hippocampus, which interacts with the cortex to re-create the memory for the spelling, pronunciation and meaning of "abacus."
7 The refurbished memory is stored in Broca's area.

In the end, we found 26 individuals for suitable control groups. Comparing Henry's results with those of these individuals revealed dramatic deficits in Henry's lexical memories, as my colleagues and I reported in a series of papers that culminated in 2009. In our tests of word meaning, for instance, the 73-year-olds without brain damage correctly responded with "a type of bean or pea" to the question "What does 'lentil' mean?" Henry, on the other hand, told us: "That's a combination word, in a way, from 'lent' and 'till' … (meaning) area and time of." Henry produced many such remarkable errors and generated fewer correct definitions than our comparison subjects, even for words that he used appropriately when he was younger. Henry also could not reliably distinguish low-frequency words from pseudowords such as "frendlihood" and "quintity." In contrast, the other 73-year-olds made accurate distinctions 82 percent of the time, and Henry himself scored at the 86 percent level on this same test at age 57.

When we instructed participants to read aloud words typed on index cards, Henry misread "triage" as "triangle," "thimble" as "tim- … tim-BO-lee" and "pedestrian" as "ped-AYE-ee-string." Henry's reading errors were far more numerous than the older adults we later tested. Apparently Henry could not remember how to pronounce multisyllabic words in which variables such as syllable stress patterns and certain letter sounds (such as whether to pronounce the e's in "pedestrian" as long or short) are unspecified.

WHAT'S IN A NAME?

HENRY'S PROBLEMS were similarly apparent in the so-called Boston naming test. In this test, people are supposed to identify common objects depicted in line drawings. If a subject cannot recall the name of the object, the experimenter provides phonological cues—for example, "it begins with 'tr'"—followed by a verification question containing the word itself: "Do you know the

Illustration by Tami Tolpa

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REMEDIES

Memory's Fountain of Youth

Like the rest of the body, the brain tends to decline with age. Yet science suggests ways to lessen the loss

First, a little perspective: not all aspects of memory decay. Older adults are just as able to understand sentences containing familiar words and to relearn forgotten information as when they were younger, though at a slightly slower rate. All behaviors are somewhat slower in older than younger individuals—a difference measured in thousandths of a second.

In some ways, cognitive function even improves with age. For example, vocabularies continue to expand up to age 80 and even beyond. As older individuals, we spontaneously use a greater variety of words and score higher on standardized vocabulary tests.

Older adults do encounter somewhat more trouble learning new uses for old words and remembering such things as a telephone number long enough to dial it. We also experience frustrating lapses in recalling the spelling of familiar, irregular words, such as "rhythm," and pronunciations—especially for the names of places and people—that we learned decades earlier.

Recent research, including my own, suggests that older adults can counteract these changes. The key is exposure. Engaging in social situations helps to protect numerous language-related, among other, facets of memory. Before meeting up with friends, we can rehearse their names so as to avoid the embarrassment of forgetting them. We can preserve our spelling and word-retrieval skills by playing games such as Scrabble in which we exercise those skills rather than engaging in passive activities such as watching television.

We can prevent the deterioration of areas of expertise—say, public speaking, chess or playing the piano—by continuing to practice or play. More generally, we can engage in lifelong learning of various forms. After all, learning and relearning—reinstating old memories—are ways the hippocampal region keeps all of us young.

—D.G.M.

MYSTERIES OF THE MIND

word 'trellis'?" Although he had been familiar with the target names at a younger age, Henry correctly named fewer pictures than others his same age, benefited less than they did from the phonological cues, and produced more erroneous answers involving incorrect speech sounds. For instance, Henry called a snail a "sidion," indicating severe degradation of his phonological memory for this familiar word.

In our spelling task, participants heard an irregularly spelled word such as "bicycle" and saw it spelled with a missing letter, as "bic_cle." They were asked to choose one of two letters ("i" or "y") to correctly fill in the blank. Henry chose the correct letter for 65 percent of the words, whereas our comparison subjects did so 82 percent of the time, suggesting extensive erosion of Henry's memories for irregularly spelled aspects of familiar words.

We next documented the trajectory of Henry's decline between his 40s and 70s. By comparing our results with those of others, we learned that Henry's lexical memories deteriorated dramatically over the years, beginning in his late 50s. For instance, in a 1983 study by psychologists John Gabrieli, Neal Cohen and Suzanne Corkin, all then at M.I.T., Henry at age 57 showed a small but reliable deficit in distinguishing low-frequency words from pseudowords. At age 73, he showed significantly greater difficulties in the same task. Similarly, Henry had no problems naming pictures at age 54, according to a 1984 study by Corkin. Yet at age 73, Henry produced dramatic word substitutions such as "compass" for "protractor," circumlocutions such as "ice clippers" for "tongs," and neologisms such as "trake" for "trellis."

In word-reading tests, Henry exhibited small deficits at age 67 in a 1993 study by Corkin and her graduate student Bradley R. Postle. In our studies, his losses were more glaring for the identical words. At age 71 he misread 67 percent of the words versus a mean of 9 percent for our control subjects. Just two years later his deficit for the same words was even greater and included new types of errors such as segment-omission errors—for instance, the reading of "affirmation" as "formation."

JUST AS A BUILDER CAN MAKE A NEW STRUCTURE OR REPAIR A DAMAGED ONE, SO COULD THE HIPPOCAMPUS CRAFT NEW MEMORIES TO REPLACE DEGRADED RECOLLECTIONS.

MEMORY MAINTENANCE

PSYCHOLOGISTS HAVE KNOWN for decades that synaptic connections in the neocortex deteriorate with age, so that memories we have stored there become increasingly weak and fragmented. The memories that suffer most are those we recall infrequently. If we have not thought about, heard or seen something recently, that information is vulnerable—and more so the older we become.

In his 50s, 60s and 70s, Henry's difficulties remembering word knowledge he rarely used or encountered became progressively worse, and the decline for him was much steeper than for typical adults of the same age and background. We reasoned, therefore, that the hippocampal complex must be involved in preserving old memories as well as making new ones. Just as a builder can make a new structure or repair a

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OUR MEMORIES are stored in the cerebral cortex as changes in the connections between neurons (*shown here*). As we age, the neural ties representing our memories weaken, and we forget.

damaged one, so could the hippocampus craft new memories to replace those that have been degraded or fragmented with time.

Such rebuilding might occur whenever someone reencounters a forgotten word or a personal anecdote from the past. In this way, recent exposure and learning could shore up a shattered memory and reduce the rate of loss. In Henry's case, this hippocampal maintenance system was defunct. Henry had no way of rejuvenating depleted memories through experience and relearning—leading to his accelerated decline.

To support this theory, we would like to determine whether other people with amnesia and hippocampal region damage eventually experience exaggerated or faster than normal degradation of memories for rarely used information. We also want to find out whether healthy older adults re-create memories that have decayed from aging and lack of use as they naturally reencounter the missing information.

From personal experience as an older adult, I believe that we can and often do refurbish fragmented recollections. When I reread my story about meeting Henry, I checked the date of our meeting by looking at my unpublished report, written soon after the experiment. Although I had been absolutely certain that I had met Henry in 1967, the report indicated 1966 as the time of the test, showing we had met one year earlier than I had remembered, a fact that I will not soon forget!

Some episodic memories are impossible to check and correct, however. As I reread my description of Henry and me climbing the stairs to our testing room, I suddenly recalled that Henry had taken out something resembling an oversize business card and proceeded to tell me a story about rifles. I can no longer retrieve the specifics of Henry's rifle story, and I have no way of revisiting this 1966 incident to renew my memory for it. As a result, the details of the rifle story will slide even further into oblivion, much like Henry's own memories did for aspects of the meaning, spelling and pronunciation of rarely used words. SA

Donald G. MacKay is professor of psychology at the University of California, Los Angeles. He earned his Ph.D. in psycholinguistics and physiological psychology at the Massachusetts Institute of Technology and is author of *The Organization of Perception and Action: A Theory for Language and Other Cognitive Skills* (1987).

MORE TO EXPLORE

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DOES BRAIN SIZE MATTER?

A recent discovery proves embarrassing to any notion of humanity's innate superiority

By Christof Koch

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WHILE "SIZE DOES NOT MATTER" IS A UNIVERSALLY preached dictum among the politically correct, everyday experience tells us that this can't be the whole story—under many conditions, it clearly does. Consider the size of Woody Allen's second favorite organ, the brain. Adjectives such as "highbrow" and "lowbrow" have their origin in the belief, much expounded by 19th-century phrenologists, of a close correspondence between a high forehead—that is, a big brain—and intelligence. Is this true? Does a bigger brain make you necessarily smarter or wiser? And is there any simple connection between the size of a nervous system, however measured, and the mental powers of the owner of this nervous system? While the answer to the former question is a conditional "yes, somewhat," the lack of any accepted answer to the second query reveals our ignorance of how intelligent behavior comes about.

IN BRIEF

Human brains vary considerably in size across adults, with males having slightly larger brains than females.

It is hard to pin down what makes the human brain exceptional among mammals—neither brain size, relative brain size nor number of neurons is unique to humans.

More intelligent people do better in life, but there is only weak correlation between brain size and intelligence, especially across species.

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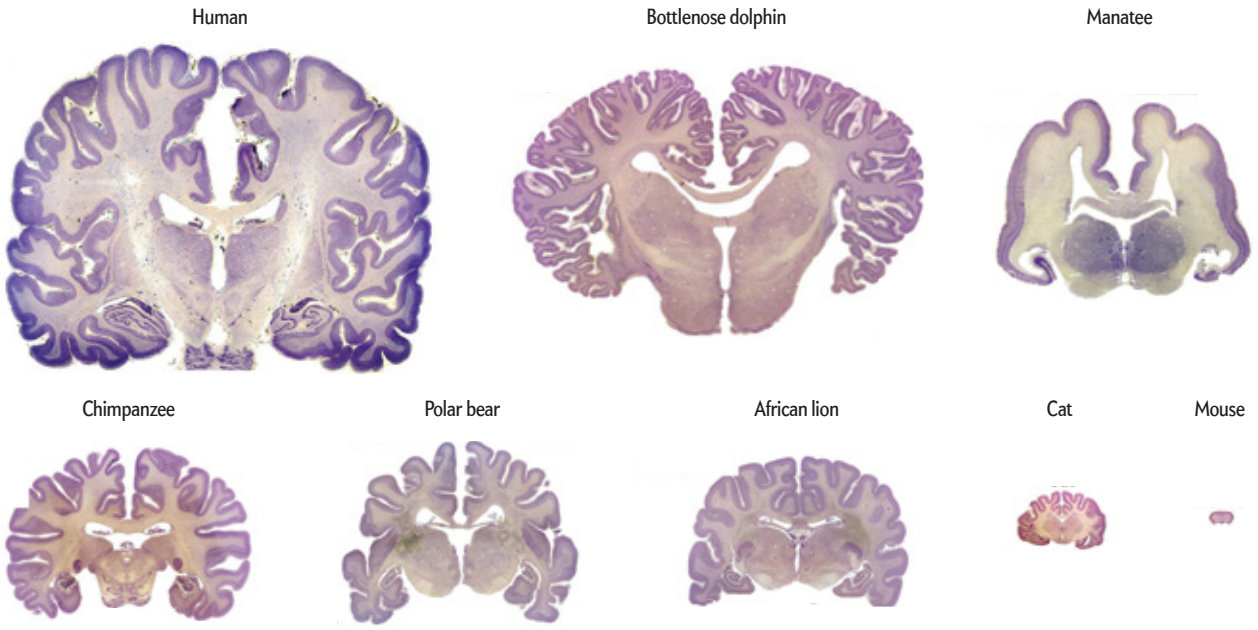
From Man to Mouse

Frontal slices of eight mammalian brains reveal the immense variety in the size of the organ and the patterning of surface convolutions that have evolved over the course of tens of millions of years. The smoothness of the manatee's brain surface contrasts with the cauliflowerlike branching in the bottlenose dolphin. Structural differences extend down to the microscopic scale. Scientists are still laboring to understand what the varying anatomy means for animal intelligence.



BIGGER IS SLIGHTLY BETTER

THE HUMAN BRAIN continues to grow until it reaches its peak size in the third to fourth decade of life. An MRI study of 46 adults of mainly European descent found that the average male had a brain volume of 1,274 cubic centimeters (cm^3) and that the average female brain measured 1,131 cm^3. Given that a quart of milk equals 946 cm^3, you could pour a bit more than that into a skull without any of it spilling out. Of course, there is considerable variability in brain volume, ranging from 1,053 to 1,499 cm^3 in men and between 975 and 1,398 cm^3 in women. As the density of brain matter is just a little bit above that of water plus some salts, the average male brain weighs about 1,325 grams, close to the proverbial three pounds often cited in U.S. texts.

RUSSIAN NOVELIST IVAN TURGENEV'S BRAIN BROKE THE TWO-KILOGRAM BARRIER. WRITER ANATOLE FRANCE'S BRAIN WAS BARELY HALF THAT.

Removing brains after their owners died revealed that Russian novelist Ivan Turgenev's brain broke the two-kilogram barrier, coming in at 2,021 grams, whereas writer Anatole France's brain could barely bring half of that weight to the scale at 1,017 grams. (Note that postmortem measures are not directly comparable to data obtained from living brains.) In other words, gross brain size varies considerably across healthy adults.

What about smarts? We all know from our day-to-day interactions that some people just don't get it and take a long time to understand a new concept; others have great mental powers, although it is impolite to dwell on such differences too much. Think of Bertie Wooster, an idle but clueless rich man, and Jeeves, his genius valet, in a series of novels by P. G. Wodehouse and their successful British adaptation to the small screen.

Individuals differ in their ability to understand new ideas, to adapt to new environments, to learn from experience, to think abstractly, to plan and to reason. Psychologists have sought to capture these differences in mental capacities via a number of closely related concepts such as general intelligence (*g*, or general cognitive ability) and fluid and crystalline intelligence. These differences in people's ability to figure things out on the spot and to retain and apply insights that they learned in the past to current circumstances are assessed by psychometric intelligence tests. These observations are reliable, in that different tests strongly correlate with one another. They are also stable across decades. That is, measures such as the intelligence quotient (IQ) can be repeatedly and reli-

PAGE 19: ALAMY; THIS PAGE: SOURCE: "THE EVOLUTION OF THE BRAIN, THE HUMAN NATURE OF CORTICAL CIRCUITS, AND INTELLECTUAL CREATIVITY," BY JAVIER DEFELIPE, IN *FRONTIERS IN NEUROANATOMY*, VOL. 5, ARTICLE NO. 29; MAY 16, 2011

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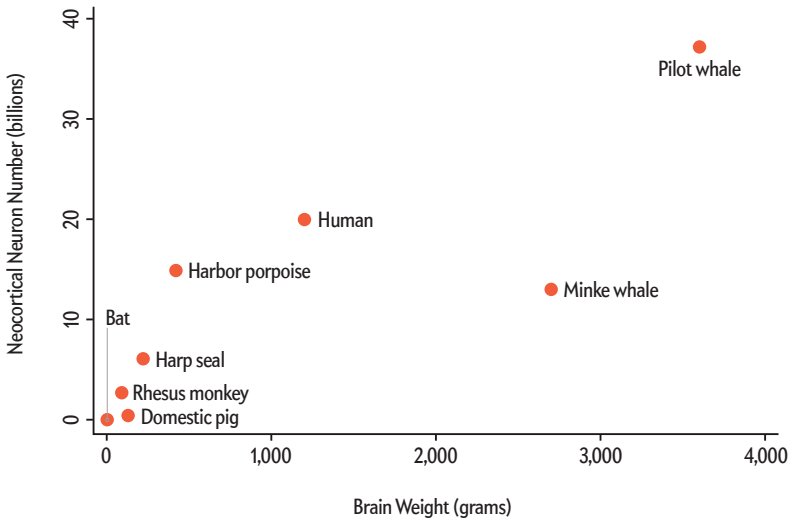
Who Has the Most Brain Cells?



The long-finned pilot whale appears to have more neurons in the neocortex—an area devoted to higher mental processes—than any other mammal, about twice the number found in the human cortex. This type of dolphin and its massive brain are shown in the two images at the right.

ably obtained from the same subjects nearly 70 years later.

Differences in general intelligence, assessed in this way, correlate with success in life, with social mobility and job performance, with health and with life span. In a study of one million Swedish men, an increase in IQ by one standard deviation, a measure of variability, was associated with an amazing 32 percent reduction in mortality. Smarter people do better in life. Whereas a high IQ may not predispose people to be happy or to understand the finer points of dating, the highly intelligent are more likely to be found among hedge-fund managers than among supermarket checkout clerks.

What about any numerical relation between brain size and intelligence? Such correlations were difficult to establish in the past when only pathologists had access to skulls and their content. With structural MRI imaging of brain anatomy, such measurements are now routine. In healthy volunteers, total brain volume weakly correlates with intelligence, with a correlation value between 0.3 and 0.4 out of a possible 1.0. In other words, brain size accounts for between 9 and 16 percent of the overall variability in general intelligence. Functional scans, used to look for brain areas linked to particular mental activities, reveal that the parietal, temporal and frontal regions of the cortex, along with the thickness of these regions, correlate with intelligence but, again, only modestly so. Thus, on average, a bigger brain is associated with somewhat higher intelligence. Whether a big brain causes high intelligence or, more likely, whether both are caused by other factors remains unknown.

THE LONG-FINNED DOLPHIN APPEARS TO HAVE MORE NEURONS IN THE NEOCORTEX THAN ANY OTHER MAMMAL.

Recent experiments take into account the particular connections among neurons in certain regions of an individual's brain, much like a neural fingerprint. They do better at predicting fluid intelligence (the capacity to solve problems in novel situations, to find and match patterns, to reason independently of specific domains of knowledge), explaining about 25 percent of the variance in this measure from one person to the next.

Our ignorance when it comes to how intelligence arises from the brain is accentuated by several further observations. As alluded to earlier, the adult male's brain is 150 grams heavier than the female's organ. In the neocortex, the part of the forebrain responsible for perception, memory, language and reasoning, this disparity translates to 23 billion neurons for men versus 19 billion for women. As no difference exists in the average IQ between the two genders, why is there a difference in the basic number of switching elements?

It is also well established that the cranial capacity of *Homo neanderthalensis,* the proverbial caveman, was 150 to 200 cm^3 bigger than that of modern humans. Yet despite their larger brain, Neandertals became extinct between 35,000 and 40,000

SOURCE: "QUANTITATIVE RELATIONSHIPS IN DELPHINID NEOCORTEX," BY HEIDI S. MORTENSEN ET AL., IN *FRONTIERS IN NEUROANATOMY*, VOL. 8, ARTICLE NO. 132. PUBLISHED ONLINE NOVEMBER 26, 2014 (*chart*); HEIDI S. MORTENSEN (*brain*); ÓLAVUR FREDERIKSEN (*pilot whale*)

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years ago, when *Homo sapiens* shared their European environment. What's the point of having big brains if your small-brained cousins outcompete you?

BRAIN SIZE ACROSS SPECIES

OUR LACK OF UNDERSTANDING of the multiplicity of causes that contribute to intelligence becomes even more apparent when looking outside the genus *Homo*. Many animals are capable of sophisticated behaviors, including sensory discrimination, learning, decision making, planning and highly adaptive social behaviors.

Consider honeybees. They can recognize faces, communicate the location and quality of food sources to their sisters via the waggle dance, and navigate complex mazes with the help of cues they store in short-term memory. And a scent blown into a hive can trigger a return to the site where the bees previously encountered this odor, a type of associative memory that guides them back and that was made famous by Marcel Proust in his *Remembrance of Things Past* (*À la Recherche du Temps Perdu*). The insect does all of this with fewer than one million neurons that weigh around one thousandth of a gram, less than one millionth the size of the human brain. Yet are we really a million times smarter? Certainly not if I look at how well we govern ourselves.

A STUDY OF PILOT WHALES PLAYS HAVOC WITH THE NOTION THAT HUMANS HAVE MORE NERVE CELLS WHERE IT COUNTS THAN ANY OTHER SPECIES ON THE PLANET.

The prevailing rule of thumb holds that the bigger the animal, the bigger its brain. After all, a bigger creature has more skin that has to be innervated and more muscles to control and requires a larger brain to service its body. Thus, it makes sense to control for overall size when studying brain magnitude. By this measure, humans have a relative brain-to-body mass of about 2 percent. What about the big mammals—elephants, dolphins and whales? Their brains far outweigh those of puny humans, up to 10 kilograms for some whales. Given their body mass, ranging from 7,000 kg (for male African elephants) up to 180,000 kg (for blue whales), their brain-to-body ratio is under a tenth of a percent. Human brains are far bigger relative to people's sizes than those of these creatures. Smugness is not in store, though. We are outclassed by shrews, molelike mammals, whose brain takes up about 10 percent of their entire body mass. Even some birds beat us on this measure. Hmm.

One small consolation is an invention of neuroanatomists called the encephalization quotient (EQ). It is the ratio of the mass of the brain of the species under investigation relative to a standard brain belonging to the same taxonomic group. Thus, if we consider all mammals and compare them against the cat as a reference animal (which therefore has an EQ of 1), people come out on top with an EQ of 7.5. Stated differently, the human brain is 7.5 times bigger than the brain of a typical mammal weighing as much as we do. Apes and monkeys come in at or below five, as do dolphins and other cetaceans. We finally made it to the top, validating our ineradicable belief in humanity's exceptionalism.

Yet it is not quite clear what all this means in terms of the cellular constituents of brains. Neuroscientists always assumed that humans have more nerve cells where it counts, in the neocortex, than any other species on the planet, no matter the size of their brain.

A 2014 study of 10 long-finned pilot whales from the Faeroe Islands plays havoc with this hypothesis. Caught as part of a local hunt in the cold waters of the North Atlantic between Scotland and Iceland, these graceful mammals—also known as blackfish—are actually dolphins. The number of nerve cells making up their highly convolved neocortex was estimated in a few sample slices and then extrapolated to the entire structure. The total came to an astonishing 37.2 billion neurons. Astonishing because this implies that the long-finned pilot whale has about twice as many neocortical neurons as humans do!

If what matters for cognitive performance is the number of neocortical neurons, these dolphins should be smarter than all other extant creatures, including us. Whereas the highly playful and social dolphins exhibit a variety of skills, including the ability to recognize themselves in a mirror, they do not possess language or any readily discernible powers of abstraction that stand out from those of other nonhuman animals. So what gives? Is the complexity of the nerve cells themselves substantially less than cells found in people, or is the way these neurons communicate or learn less sophisticated? We don't know.

People forever ask for *the* single thing that distinguishes humans from all other animals, on the supposition that this one magical property would explain our evolutionary success—the reason we can build vast cities, put people on the moon, write *Anna Karenina* and compose *Eroica*. For a while it was assumed that the secret ingredient in the human brain could be a particular type of neuron, so-called spindle or von Economo neurons, after Baron Constantin von Economo (1876–1931).

But we now know that not only great apes but also whales, dolphins and elephants have these neurons in their frontal cortex. So it is not brain size, relative brain size or absolute number of neurons that distinguishes us. Perhaps our wiring has become more streamlined, our metabolism more efficient, our synapses more sophisticated.

As Charles Darwin surmised, it is very likely a combination of a great many different factors that jointly, over the gradual course of evolution, made us distinct from other species. We are unique, but so is every other species, each in its own way. SA

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MYSTERIES OF THE MIND

MORE TO EXPLORE

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why we have free will

Neurons fire in your head before you become aware that you have made a decision. But this discovery does not mean you are a "biochemical puppet"

By Eddy Nahmias

ONE NIGHT LAST FALL I LAY AWAKE WONDERING HOW I should begin this essay. I imagined a variety of ways I could write the first sentence and the next and the one after that. Then I thought about how I could tie those sentences to the following paragraph and the rest of the article. The pros and cons of each of those options circled back and forth in my head, keeping me from drifting off to sleep. As this was happening, neurons were buzzing away in my brain. Indeed, that neural activity explains *why* I imagined these options, and it explains why I am writing these very words. It also explains why I have free will.

Illustration by Simon Prades

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Increasingly, neuroscientists, psychologists and pundits say that I am wrong. Invoking a number of widely cited neuroscientific studies, they claim that unconscious processes drove me to select the words I ultimately wrote. Their arguments suggest our conscious deliberation and decisions happen only after neural gears below the level of our conscious awareness have already determined what we will choose. And they conclude that because "our brains make us do it"—choosing for us one option over another—free will is nothing more than an illusion.

The experiments most often cited to show that our brains take charge behind the scenes were carried out by the late Benjamin Libet in the 1980s at the University of California, San Francisco. There he instructed study participants outfitted with electrodes on their heads to flick their wrists whenever they felt like it. The electrodes detected fluctuations in electrical activity called readiness potentials that occurred about half a second before people made the flicking motion. But participants became aware of their intentions to move only about a quarter of a second before the movement, leading to the conclusion that their brains had decided before they became aware of what had happened. In essence, unconscious brain processes were in the driver's seat.

More recent studies using functional MRI have suggested the unconscious roots of our decisions begin even earlier. In research published in 2013, neuroscientist John-Dylan Haynes of the Bernstein Center for Computational Neuroscience Berlin and his colleagues had volunteers decide whether to add or subtract two numbers while in the fMRI scanner. They found patterns of neural activity that were predictive of whether subjects would choose to add or subtract that occurred four seconds before those subjects were aware of making the choice.

These studies—and others like them—have led to sweeping pronouncements that free will is dead. "Our decisions are predetermined unconsciously a long time before our consciousness kicks in," Haynes commented to *New Scientist,* while adding that "it seems that the brain is making the decision before the person." Others share his opinion. Evolutionary biologist Jerry Coyne has written: "So it is with all of our … choices: not one of them results from a free and conscious decision on our part. There is no freedom of choice, no free will." Neuroscientist Sam Harris has concluded from these findings that we are "biochemical puppets": "If we were to detect [people's] conscious choices on a brain scanner seconds before they were aware of them … this would directly challenge their status as conscious agents in control of their inner lives."

But does the research really show that all our conscious deliberation and planning is just a by-product of unconscious brain activity, having no effect on what we do later on? No, not at all. For many reasons, others, such as philosopher Alfred R. Mele of Florida State University, and I argue that people who insist free will is a mirage are misguided.

NOT SO FAST

I CALL THOSE who contend that science shows that free will is an illusion "willusionists." There are many reasons to be wary of the willusionists' arguments. First, neuroscience currently lacks the technical sophistication to determine whether neural activity underlying our imagining and evaluating of future options has any impact on which option we then carry out minutes, hours or days later. Instead the research discussed by willusionists fails to clearly define the border between conscious and unconscious actions.

Consider the Libet experiment. It began with study participants preparing consciously to make a series of repetitive and unplanned actions. When the experiment began, they flexed their wrists when a desire arose spontaneously. The neural activity involved in the conscious planning presumably influenced the later unconscious initiation of movements, revealing an interaction between conscious and unconscious brain activity.

Similarly, the 2011 Haynes study, in which people randomly picked whether to add or subtract over the course of many trials, fails to provide convincing evidence against free will. Early brain activity that occurred four seconds before participants were aware of making a choice may be an indication of unconscious biases toward one choice or the other.

But this early brain activity predicted a choice with an accuracy only 10 percent better than random chance. Brain activity cannot, in general, *settle* our choices four seconds before we act, because we can react to changes in our situation in less time than that. If we could not, we would all have died in car crashes by now! Unconscious neural activity, however, can prepare us to take an action by cuing us to consciously monitor our actions to let us adjust our behavior as it occurs.

Willusionists also point to psychological research showing that we have less conscious control over our actions than we think. It is true that we are often influenced unknowingly by subtle features of our environment and by emotional or cognitive biases. Until we understand them, we are not free to try to counteract them. This is one reason I think we have less free will than many people tend to believe. But there is a big difference between having less and none at all.

The Libet and Haynes research deals with choices that people make without conscious deliberation at the time of action. Everyone performs repetitive or habitual behaviors, sometimes quite sophisticated ones that do not require much thought because the behaviors have been learned. You put your key in the lock. A shortstop dives for a ground ball. A pianist becomes immersed in playing Beethoven's *Moonlight Sonata*.

The reflexive turning of the key, the lunging for the ball, or the depressing of the white and black keys requires a particular type of mental processing. What I was doing on that sleepless night—conscious consideration of alternative options—is a wholly different activity from engaging in practiced routines.

IN BRIEF

A major question in neuroscience, in philosophy and in broader public debate is whether the assumption that we have free will is fundamentally misconstrued. If it is, many legal and moral precepts that are the basis for our social institutions are subject to challenge.

Doubts exist because of sophisticated experiments in recent decades that have shown that the brain initiates some actions before we become consciously aware that a decision has been made. If this is so, what role, if any, does free will play?

People may have less free will than they think, but that does not mean they have none at all. A number of recent experiments by social psychologists have shown that conscious reasoning and intentions have a significant impact on our actions.

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A body of psychological research shows that conscious, purposeful processing of our thoughts really does make a difference to what we do.

This work indicates that intentions we formulate to carry out specific tasks in particular circumstances—what psychologists call "implementation intentions"—increase the likelihood that we will complete the planned behavior. A study performed by psychologist Peter Gollwitzer of New York University and his colleagues revealed that dieters who consciously formed an intention to ignore thoughts about tempting foods whenever they came to mind then ate less of those foods than those dieters who simply set the goal to lose weight.

Psychologist Roy F. Baumeister of Florida State University and his colleagues have demonstrated that conscious reasoning improves performance on logical and linguistic tasks and that it helps in learning from past mistakes and overriding impulsive behaviors. In addition, psychologist Walter Mischel of Columbia University has found that our ability to willfully distract ourselves from a temptation is crucial for self-control.

Every one of us carries out actions every day that we have consciously planned for ourselves. It is possible that the neural activity that carries out this planning has no effect on what we do or that it just concocts stories after the fact to explain to ourselves and others what we did. But that would make little evolutionary sense. The brain makes up only 2 percent of the human body's weight but consumes 20 percent of its energy. There would be strong evolutionary pressure against neural processes that enable intricate conscious thought yet are irrelevant to our behavior. The brain circuits responsible for my imagining that this is the best way to write this essay are likely causing it to turn out this way.

FREE WILL IN THE BRAIN?

WILLUSIONISTS, however, suggest this internalized brain processing simply cannot count as free will. They often say that people who believe in free will must be "dualists" who are convinced that the mind somehow exists as a nonphysical entity, separate from the brain. "Free will is the idea that we make choices and have thoughts independent of anything remotely resembling a physical process," wrote neuroscientist Read Montague in 2008. And Coyne has claimed that "true 'free will' … would require us to step outside of our brain's structure and modify how it works."

It is true that some people think of free will in this way. But there is no good reason to do so. Most philosophical theories develop a view of free will that is consistent with a scientific understanding of human nature. And despite willusionists' claims, studies suggest that most people accept that we can have free will even if our mental activity is carried out entirely by brain activity. If most people are not dualists about free will, then it is a mistake to tell them that free will is an illusion based on the scientific view that dualism is false.

One way to test people's assumptions about free will is to describe the possibility of brain-imaging technology that would allow perfect prediction of actions based on information about prior brain activity. In fact, Harris has suggested this scenario "would expose this feeling [of free will] for what it is: an *illusion*."

To see whether people's belief in free will would be challenged by the knowledge that the brain is engaged in unconscious information processing that predicts behavior, Jason Shepard of Emory University, Shane Reuter of Washington University in St. Louis and I performed a series of experiments in which we presented people with detailed scenarios describing futuristic brain-imaging technology, as posited by Harris.

Hundreds of students at Georgia State University participated in the studies. They read about a woman named Jill who, in the distant future, wore a brain-imaging cap for a month. Using information from the brain scanner, neuroscientists predicted everything she thought and did, even when she tried to fool the system. The scenario concluded that "these experiments confirm that all human mental activity just *is* brain activity such that everything that any human thinks or does could be predicted ahead of time based on their earlier brain activity."

More than 80 percent of the participants reported that they believed that such future technology was possible, yet 87 percent of them responded that Jill still had free will. They were also asked whether the existence of such technology would indicate that individuals lack free will. Roughly 75 percent disagreed. Further results showed that a significant majority felt that as long as the technology did not allow people's brains to be manipulated such that their decisions could be controlled by others, they would have free will and be morally responsible for their behavior.

Most participants in the experiments seem to think that the hypothetical brain scanner is just recording the brain activity that is Jill's conscious reasoning and consideration about what to decide. Rather than taking this to mean that Jill's brain is making her do something—and that she has no free will—they may just be thinking that the brain scanner is simply detecting how free will works in the brain.

Why, then, do willusionists believe the opposite? It may have to do with the current state of knowledge. Until neuroscience is able to explain consciousness—which will require a theory to explain how our mind is neither reducible to, nor distinct from, the workings of our brain—it is tempting to think, as the willusionists seem to, that if the brain does it all, there is nothing left for the conscious mind to do.

As neuroscience advances and imaging technology improves, these developments should help reveal more precisely how much conscious control we have and to what extent our actions are governed by processes beyond our control. Finding resolutions for these questions about free will is important. Our legal system—and the moral basis for many of our society's institutions—requires a better understanding of when people are—and are not—responsible for what they do. SA

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WHY GOOD THOUGHTS BLOCK BETTER ONES

While we are working through a problem, the brain's tendency to stick with familiar ideas can literally blind us to superior solutions

By Merim Bilalić and Peter McLeod

Illustration by Danny Schwartz

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IN A CLASSIC 1942 EXPERIMENT, AMERICAN PSYCHOLOGIST ABRAHAM LUCHINS ASKED volunteers to do some basic math by picturing water jugs in their mind. Given three empty containers, for example, each with a different capacity—21, 127 and three units of water—the participants had to figure out how to transfer liquid between the containers to measure out precisely 100 units. They could fill and empty each jug as many times as they wanted, but they had to fill the vessels to their limits. The solution was to first fill the second jug to its capacity of 127 units, then empty it into the first to remove 21 units, leaving 106, and finally to fill the third jug twice to subtract six units for a remainder of 100. Luchins presented his volunteers with several more problems that could be solved with essentially the same three steps; they made quick work of them. Yet when he gave them a problem with a simpler and faster solution than the previous tasks, they failed to see it.

This time Luchins asked the participants to measure out 20 units of water using containers that could hold 23, 49 and three liquid units. The solution is obvious, right? Simply fill the first jug and empty it into the third one: 23 – 3 = 20. Yet many people in Luchins's experiment persisted to solve the easier problem the old way, emptying the second container into the first and then into the third twice: 49 – 23 – 3 – 3 = 20. And when Luchins gave them a problem that had a two-step solution—but could not be solved using the three-step method to which the volunteers had become accustomed—they gave up, saying it was impossible.

The water jug experiment is one of the most famous examples of the *Einstellung* effect: the human brain's dogged tendency to stick with a familiar solution to a problem—the one that first comes to mind—and to ignore alternatives. Often this type of thinking is a useful heuristic. Once you have hit on a successful method to, say, peel garlic, there is no point in trying an array of different techniques every time you need a new clove. The trouble with this cognitive shortcut, however, is that it sometimes blinds people to more efficient or appropriate solutions than the ones they already know.

Building on Luchins's early work, psychologists replicated the *Einstellung* effect in many different laboratory studies with both novices and experts exercising a range of mental abilities, but exactly how and why it happened was never clear. Recently, by recording the eye movements of highly skilled chess players, we have solved the mystery. It turns out that people under the influence of this cognitive shortcut are literally blind to certain details in their environment that could provide them with a more effective solution. New research also suggests that many different cognitive biases discovered by psychologists over the years—those in the courtroom and the hospital, for instance—are in fact variations of the *Einstellung* effect.

BACK TO SQUARE ONE

SINCE AT LEAST THE EARLY 1990S, psychologists have studied the *Einstellung* effect by recruiting chess players of varying skill levels, from amateur to grand master. In such experiments, researchers have presented players with specific arrangements of chess pieces on virtual chessboards and asked them to achieve a checkmate in as few moves as possible. Our own studies, for instance, provided expert chess players with scenarios in which they could accomplish a checkmate using a well-known sequence called "smothered mate." In this five-step maneuver, the queen is sacrificed to draw one of the opponent's pieces onto a square to block off the king's escape route. The players also had the option to checkmate the king in just three moves with a much less familiar sequence. As in Luchins's water jug studies, most of the players failed to find the more efficient solution.

During some of these studies, we asked the players what was going through their mind. They said they had found the smoth-

IN BRIEF

The *Einstellung* effect is the brain's tendency to stick with the most familiar solution to a problem and stubbornly ignore alternatives.

Psychologists have known about this mental phenomenon since the 1940s, but only now do they have a solid understanding of how it happens.

In recent eye-tracking experiments, familiar ideas blinded chess players to areas of a chessboard that would have provided clues to better solutions.

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ered mate solution and insisted they were searching for a shorter one, to no avail. But the verbal reports offered no insight into why they could not find the swifter solution. In 2007 we decided to try something a little more objective: tracking eye movements with an infrared camera. Which part of the board people looked at and how long they looked at different areas would unequivocally tell us which aspects of the problem they were noticing and ignoring.

In this experiment, we followed the gaze of five expert chess players as they examined a board that could be solved either with the longer smothered mate maneuver or with the shorter three-move sequence. After an average of 37 seconds, all the players insisted that the smothered mate was the speediest possible way to corner the king. When we presented them with a board that could be solved only with the three-sequence move, however, they found it with no problem. And when we told the players that this same swift checkmate had been possible in the previous chessboard, they were shocked. "No, it is impossible," one player exclaimed. "It is a different problem; it must be. I would have noticed such a simple solution." Clearly, the mere possibility of the smothered mate move was stubbornly masking alternative solutions. In fact, the *Einstellung* effect was powerful enough to temporarily lower expert chess masters to the level of much weaker players.

ANY DATA THAT DO NOT FIT THE SOLUTION OR THEORY WE HAVE ALREADY CLUNG TO ARE IGNORED OR DISCARDED.

The infrared camera revealed that even when the players said they were looking for a faster solution—and indeed believed they were doing so—they did not actually shift their gaze away from the squares they had already identified as part of the smothered mate move. In contrast, when presented with the one-solution chessboard, players initially looked at the squares and pieces important for the smothered mate and, once they realized it would not work, directed their attention toward other squares and soon hit on the shorter solution.

BASIS FOR BIAS

IN 2013 Heather Sheridan, now at the University of Albany, SUNY, and Eyal M. Reingold of the University of Toronto published studies that corroborate and complement our eye-tracking experiments. They presented 17 novice and 17 expert chess players with two different situations. In one scenario, a familiar checkmate maneuver such as the smothered mate was advantageous but second best to a distinct and less obvious solution. In the second situation, the more familiar sequence would be a clear blunder. As in our experiments, once amateurs and master chess players locked onto the helpful familiar maneuver, their eyes rarely drifted to squares that would clue them in to the better solution. When the well-known sequence was obviously a mistake, however, all the experts (and most of the novices) detected the alternative.

The *Einstellung* effect is by no means limited to controlled experiments in the lab or even to mentally challenging games like chess. Rather it is the basis for many cognitive biases. English philosopher, scientist and essayist Francis Bacon was especially eloquent about one of the most common forms of cognitive bias in his 1620 book *Novum Organum:* "The human understanding when it has once adopted an opinion … draws all things else to support and agree with it. And though there be a greater number and weight of instances to be found on the other side, yet these it either neglects or despises, or else by some distinction sets aside and rejects.… Men … mark the events where they are fulfilled, but where they fail, though this happen much oftener, neglect and pass them by. But with far more subtlety does this mischief insinuate itself into philosophy and the sciences, in which the first conclusion colours and brings into conformity with itself all that comes after."

In the 1960s English psychologist Peter Wason gave this particular bias a name: "confirmation bias." In controlled experiments, he demonstrated that even when people attempt to test theories in an objective way, they tend to seek evidence that confirms their ideas and to ignore anything that contradicts them.

In *The Mismeasure of Man,* for example, Stephen Jay Gould of Harvard University reanalyzed data cited by researchers trying to estimate the relative intelligence of different racial groups, social classes and sexes by measuring the volumes of their skulls or weighing their brains, on the assumption that intelligence was correlated with brain size. Gould uncovered massive data distortion. On discovering that French brains were on average smaller than their German counterparts, French neurologist Paul Broca explained away the discrepancy as a result of the difference in average body size between citizens of the two nations. After all, he could not accept that the French were less intelligent than the Germans. Yet when he found that women's brains were smaller than those in men's noggins, he did not apply the same correction for body size, because he did not have any problem with the idea that women were less intelligent than men.

Somewhat surprisingly, Gould concluded that Broca and others like him were not as reprehensible as we might think. "In most cases discussed in this book we can be fairly certain that biases … were unknowingly influential and that scientists believed they were pursuing unsullied truth," Gould wrote. In other words, just as we observed in our chess experiments, comfortably familiar ideas blinded Broca and his contemporaries to the errors in their reasoning. Here is the real danger of the *Einstellung* effect. We may believe that we are thinking in an open-minded way, completely unaware that our brain is selectively directing attention away from aspects of our environment that could inspire new thoughts. Any data that do not fit the solution or theory we have already clung to are ignored or discarded.

The surreptitious nature of confirmation bias has unfortunate consequences in everyday life, as documented in studies on decision making among doctors and juries. In a review of errors in medical thought, physician Jerome Groopman noted that in most cases of misdiagnosis, "the doctors didn't stumble because of their ignorance of clinical facts; rather, they missed diagnoses because they fell into cognitive traps." When doctors inherit a patient from another doctor, for example, the first clinician's diagnosis can blind the second to important and contradictory details of the patient's health that might change the diagnosis. It is easier to just accept the diagnosis—the "solution"—that is already in front of them than to rethink the entire situation. Similarly, radiologists examining chest x-rays often fixate on the

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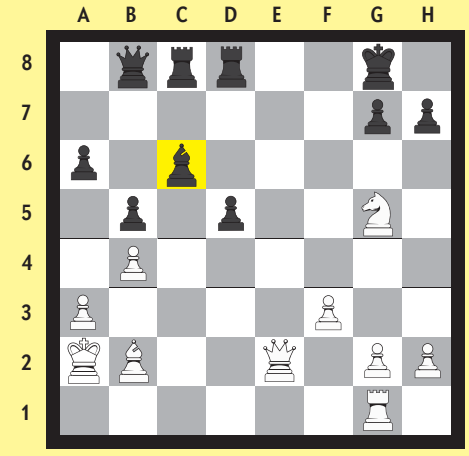
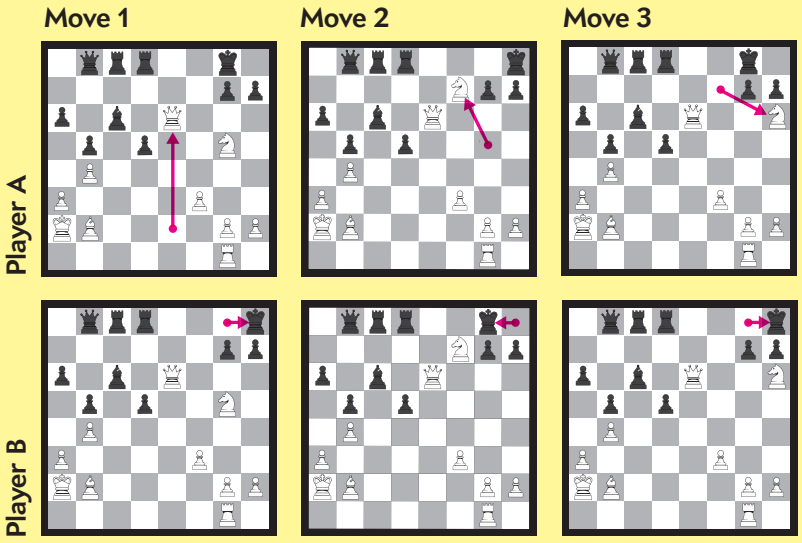
Much More Than Meets the Eye

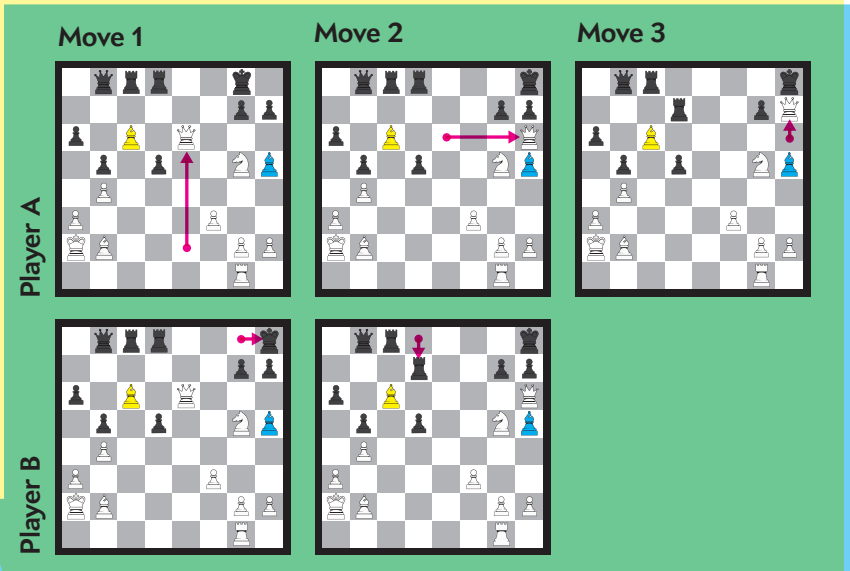
The intellectually demanding game of chess has proved a wonderful way for psychologists to study the *Einstellung* effect—the brain's tendency to stick with solutions it already knows rather than looking for potentially superior ones. Experiments have shown that this cognitive bias literally changes how even expert chess players see the board in front of them.

MYSTERIES OF THE MIND

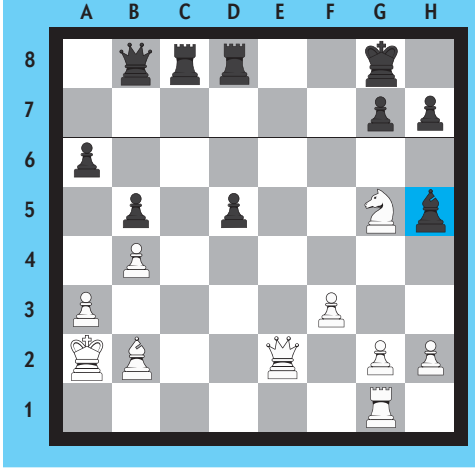
Two-Solution Problem







One-Solution Problem



Chess Masters Fail to See the Quickest Path to Victory

In a well-known five-sequence move called smothered mate (*yellow*), player A begins by moving his queen from E2 to E6, backing player B's king into a corner. Player A then repeatedly threatens to take B's king with a knight, forcing player B to dodge. As an act of deliberate sacrifice, player A moves his queen adjacent to B's king, allowing player B to take the queen with a rook. To end the game, player A moves his knight to F7, boxing in B's king with no chance of escape. In recent experiments, psychologists presented master chess players with the two-solution board shown, which could be won using either the smothered mate or a much swifter three-step solution (*green*). The players were told to achieve checkmate as quickly as possible, but once they recognized the smothered mate as a possibility, they became seemingly incapable of noticing the more efficient strategy. When presented with a nearly identical board on which the position of one bishop had shifted (*blue*), eliminating the smothered mate as an option, the players did recognize the speedier solution, however.

Illustration by George Retseck

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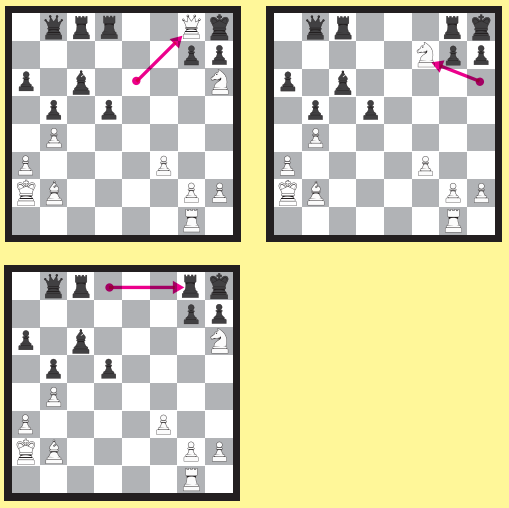
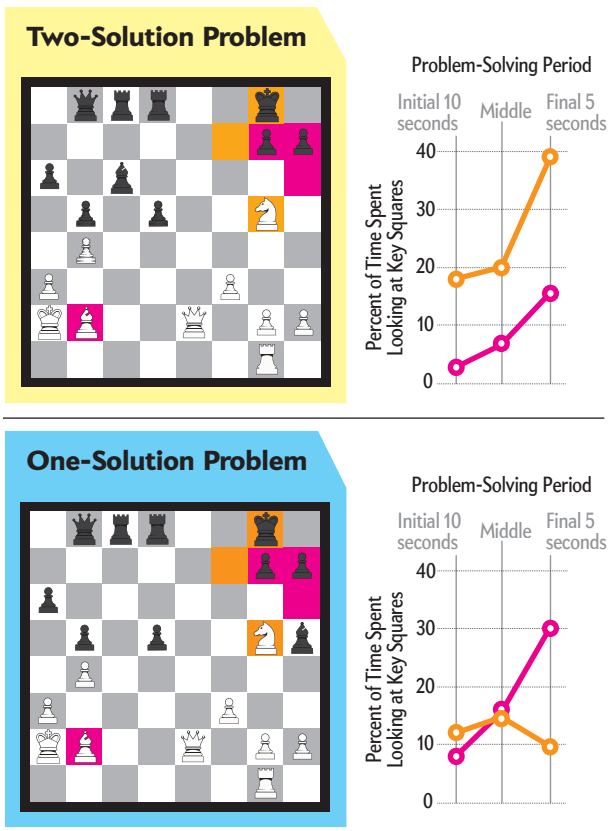


The Explanation: Tunnel Vision

Eye-tracking devices revealed that as soon as chess players hit on the smothered mate as a solution, they spent far more time looking at squares relevant to that familiar maneuver (*orange*) than at squares pertinent to the more efficient three-step sequence (*magenta*), despite insisting that they were searching for alternatives. Conversely, when the smothered mate was not viable, the players' gaze shifted to regions of the chessboard crucial to the swifter strategy.



first abnormality they find and fail to notice further signs of illness that should be obvious, such as a swelling that could indicate cancer. If those secondary details are presented alone, however, radiologists see them right away.

Related studies have revealed that jurors begin to decide whether someone is innocent or guilty long before all the evidence has been presented. In turn, their initial impressions of the defendant change how they weigh subsequent evidence and even their memory of evidence they saw before. Likewise, if an interviewer finds a candidate to be physically attractive, he or she will automatically perceive that person's intelligence and personality in a more positive light, and vice versa. These biases, too, are driven by the *Einstellung* effect. It is easier to make a decision about someone if one maintains a consistent view of that person rather than sorting through contradictory evidence.

Can we learn to resist the *Einstellung* effect? Perhaps. In our chess experiments and the follow-up experiments by Sheridan and Reingold, some exceptionally skilled experts, such as grand masters, did in fact spot the less obvious optimal solution even when a slower but more familiar sequence of moves was possible. This suggests that the more expertise someone has in their field—whether chess, science or medicine—the more immune they are to cognitive bias.

But no one is completely impervious; even the grand masters failed when we made the situation tricky enough. Actively remembering that you are susceptible to the *Einstellung* effect is another way to counteract it. When considering the evidence on, say, the relative contribution of man-made and naturally occurring greenhouse gases to global temperature, remember that if you already think you know the answer, you will not judge the evidence objectively. Instead you will notice evidence that supports the opinion you already hold, evaluate it as stronger than it really is and find it more memorable than evidence that does not support your view.

We must try and learn to accept our errors if we sincerely want to improve our ideas. English naturalist Charles Darwin came up with a remarkably simple and effective technique to do just this. "I had … during many years, followed a golden rule, namely, that whenever a published fact, a new observation or thought came across me, which was opposed by my general results, to make a memorandum of it without fail and at once," he wrote. "For I had found by experience that such facts and thoughts were far more apt to escape from memory than favourable ones." SA

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WHERE AM I? WHERE AM I GOING?

Scientists are discovering how the brain navigates

By May-Britt Moser and Edvard I. Moser

Illustration by Viktor Koen

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OUR ABILITY TO PILOT A CAR OR AIRPLANE—OR EVEN TO WALK THROUGH city streets—has been completely transformed by the invention of the Global Positioning System (GPS). How did we navigate, though, before we had GPS? Recent work has shown that the mammalian brain uses an incredibly sophisticated GPS-like tracking system of its own to guide us from one location to the next. Like the GPS in our phones and cars, our brain's system assesses where we are and where we are heading by integrating multiple signals relating to our position and the passage of time. The brain normally makes these calculations with minimal effort, so we are barely conscious of them. It is only when we get lost or when our navigation skills are compromised by injury or a neurodegenerative disease that we get a glimpse of how critical this mapping-and-navigation system is to our existence.

The ability to figure out where we are and where we need to go is key to survival. Without it, we, like all animals, would be unable to find food or reproduce. Individuals—and, in fact, the entire species—would perish.

The sophistication of the mammalian system becomes particularly clear when contrasted to those of other animals. The simple roundworm *Caenorhabditis elegans,* which has just 302 neurons, navigates almost solely in response to olfactory signals, following the path of an increasing or decreasing odor gradient.

Animals with more sophisticated nervous systems, such as desert ants or honeybees, find their way with the help of additional strategies. One of these methods is called path integration, a GPS-like mechanism in which neurons calculate position based on constant monitoring of the animal's direction and speed of movement relative to a starting point—a task carried out without reference to external cues such as physical landmarks. In vertebrates, especially in mammals, the repertoire of behaviors that enable an animal to locate itself in its environment has expanded still further.

More than any other class of animals, mammals rely on the capacity to form neural maps of the environment—patterns of electrical activity in the brain in which groups of nerve cells fire in a way that reflects the layout of the surrounding environment and an animal's position in it. The formation of such mental maps is mostly thought to occur in the cortex, the brain's wrinkled upper layers that developed quite late in evolution.

Over the past few decades researchers have gained a deep understanding of just how the brain forms and then revises these maps as an animal moves. The recent work, conducted mostly in rodents, has revealed that the navigation systems consist of several specialized cell types that continuously calculate an animal's location, the distance it has traveled, the direction

IN BRIEF

Determining where we are in relation to our surroundings—streets, trees, walls or other landmarks around us—remains an essential skill without which our own survival, or even that of our species, would rapidly be endangered.

Networks of cells lodged deep within the brain work together to assemble an internal mental map of our environment that enables us to find our way from place to place, as if these cells equated to a biological Global Positioning System.

Regions of the brain involved with pathfinding are also intimately connected to the formation of new memories. When these neural tracts malfunction, they can produce the severe disorientation experienced by a patient with Alzheimer's disease.

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it is moving and its speed. Collectively these different cells form a dynamic map of local space that not only operates in the present but also can be stored as a memory for later use.

A NEUROSCIENCE OF SPACE

THE STUDY of the brain's spatial maps began with Edward C. Tolman, a psychology professor at the University of California, Berkeley, from 1918 to 1954. Before Tolman's work, laboratory experiments in rats seemed to suggest that animals find their way around by responding to—and then memorizing—successive stimuli along the path they move. In learning to run a maze, for instance, they were thought to recall sequences of turns they made from the maze's start to its end. This idea, however, did not take into account that the animals might visualize an overall picture of the entire maze to be able to plan the best route.

Tolman broke radically with prevailing views. He had observed rats take shortcuts or make detours, behaviors that would not be expected if they had learned only one long sequence of behaviors. Based on his observations, he proposed that animals form mental maps of the environment that mirror the spatial geometry of the outer world. These cognitive maps did more than help animals to find their way; they also appeared to record information about the events that the animals experienced at specific locales.

Tolman's ideas, proposed for the first time around 1930, remained controversial for decades. Acceptance came slowly, in part because they were based entirely on observing the behavior of experimental animals, which could be interpreted in many ways. Tolman did not have the concepts or tools to test whether an internal map of the environment actually existed in an animal's brain.

It took about 40 years before direct evidence for such a map appeared in studies of neural activity. In the 1950s progress in the development of microelectrodes made it possible to monitor electrical activity from individual neurons in awake animals. These very thin electrodes enabled researchers to identify the firing of single neurons as the animals went about their business. A cell "fires" when it triggers an action potential—a short-lasting change in the voltage across the neuronal cell membrane. Action potentials cause neurons to release neurotransmitter molecules that convey signals from one neuron to another.

John O'Keefe of University College London used microelectrodes to monitor action potentials in rats in the hippocampus, an area of the brain known for decades to be important for memory functions. In 1971 he reported that neurons there fired when a rat in a box spent time at a certain location—thus, he called them place cells. O'Keefe observed that different place cells fired at different locations in the box and that the firing pattern of the cells collectively formed a map of locations in the box. The combined activity of multiple place cells could be read out from the electrodes to identify the animal's precise location at any given time. In 1978 O'Keefe and his colleague Lynn Nadel, now at the University of Arizona, suggested that place cells were, in fact, an integral part of the cognitive map Tolman had envisaged.

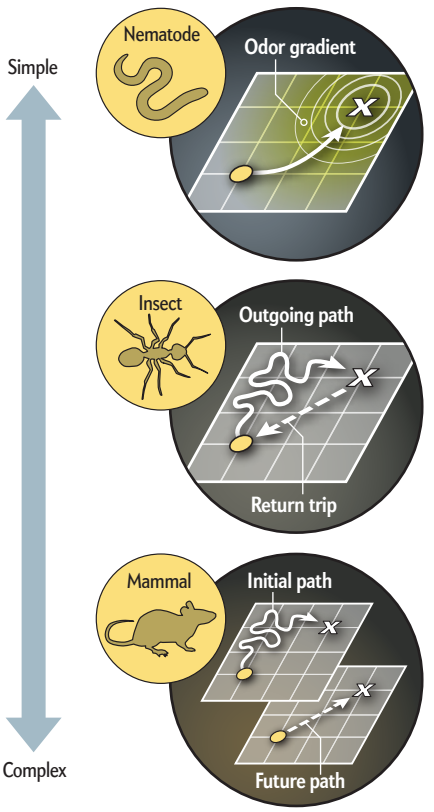
A CORTICAL MAP

THE DISCOVERY of place cells opened a window into the deepest parts of the cortex, in areas farthest away from the sensory cortices (those that receive inputs from the senses) and from the

NATURE'S NAVIGATORS

The Nervous System's Incredible Pathfinding Skills

Survival for any species requires an ability to take into account the surrounding environment and to make a calculation, even a crude one, of where an animal has been, where it is and where it is going. On higher rungs of the evolutionary chain, many species have developed "path integration" systems that allow them to perform this task without the need to locate where they are by referencing external landmarks. Mammals have found an even more elaborate solution that uses internalized mental maps.



Tracing a Smell

The simple roundworm *Caenorhabditis elegans* exhibits perhaps the most basic animal navigation system. The worm world is organized according to smell. Equipped with a mere 302 neurons, it pushes itself straight ahead toward a food source by sensing ever increasing levels of an odor.

Internal GPS

Evolution has equipped even some insects and other arthropods with elaborate path-integration capabilities. They can monitor internally their speed and direction relative to a starting point. This allows them to find more efficient means of traveling a given route—a direct return instead of the zigs and zags traversed on an outbound journey.

Mental Maps

Mammals have evolved still more intricate orienteering skills in which neurons fire in their brain in sequences that mirror the routes they travel. These networks of neurons make up mental maps of the physical world. Animals store memories of past journeys and use them for the planning of future trips.

Illustrations by Jen Christiansen

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motor cortex (which emits the signals that initiate or control movement). At the end of the 1960s, when O'Keefe started his work, knowledge about when neurons switched on and off was largely restricted to areas called the primary sensory cortices, where neural activity was controlled directly by such sensory inputs as light, sound and touch.

Neuroscientists of that era speculated that the hippocampus was too far removed from the sensory organs to process their inputs in any manner that could easily be understood from a microelectrode recording. The discovery of cells in the hippocampus that created a map of an animal's immediate environment dashed that speculation.

Even though the finding was remarkable and suggested a role for place cells in navigation, no one knew what that role might be for decades after their discovery. Place cells were in an area of the hippocampus, called CA1, that was the end point in a signaling chain originating elsewhere in the hippocampus. It was hypothesized that place cells received many of the critical navigation-related computations from other hippocampal regions. In the early 2000s the two of us decided to explore this idea further in the new lab we had set up at the Norwegian University of Science and Technology in Trondheim. This pursuit ultimately led to a major discovery.

HUMANS AND OTHER MAMMALS FORM INTERNAL MAPS OF THE ENVIRONMENT—PATTERNS OF NEURAL ACTIVITY IN WHICH BRAIN CELLS FIRE TO REFLECT WHERE AN ANIMAL IS AND WHERE IT IS POSITIONED IN RELATION TO ITS SURROUNDINGS.

In collaboration with Menno Witter, now at our institute, and a set of highly creative students, we began by using microelectrodes to monitor the activity of place cells in the rat hippocampus after we had disrupted part of a neuronal circuit there known to feed information to these cells. We expected the work to confirm that this circuit was important to the proper functioning of the place cells. To our surprise, the neurons at the end of that circuit, in CA1, still fired when the animals arrived at specific locations.

Our team's inescapable conclusion was that place cells did not depend on this hippocampal circuit to gauge an animal's bearings. Our attention then turned to the only neural pathway that had been spared by our intervention: the direct connections to CA1 from the entorhinal cortex, an adjoining area that provides an interface to the rest of the cortex.

In 2002 we inserted microelectrodes in the entorhinal cortex, still in a collaboration with Witter, and began recording as the animals performed tasks that were similar to the ones we had used for our place cell studies. We guided electrodes into an area of the entorhinal cortex having direct connections to the parts of hippocampus where place cells had been recorded in almost every study before ours. Many cells in the entorhinal cortex turned out to fire when an animal was at a particular spot in the enclosure, much like the place cells in the hippocampus do. But unlike a place cell, a single cell in the entorhinal cortex fired, not only at one location visited by a rodent but at many.

The most striking property of these cells, though, was the way they fired. Their pattern of activity became obvious to us only when, in 2005, we increased the size of the enclosure in which we were recording. After expanding it to a certain size, we found that the multiple locations at which an entorhinal cell fired formed the vertices of a hexagon. At each vertex, the cell, which we called a grid cell, fired when the animal passed over it.

The hexagons, which covered the entire enclosure, appeared to form the individual units of a grid—similar to the squares formed by the coordinate lines on a road map. The firing pattern raised the possibility that grid cells, unlike place cells, provide information about distance and direction, helping an animal to track its trajectory based on internal cues from the body's motions without relying on inputs from the environment.

Several aspects of the grid also changed as we examined the activity of cells in different parts of the entorhinal cortex. At the dorsal part, near the top of this structure, the cells generated a grid of the enclosure that consisted of tightly spaced hexagons. The size of the hexagons increased in a series of steps—or modules—as one moved toward the lower, or ventral, part of the entorhinal cortex. The hexagonal grid elements in each module had a unique spacing.

The spacing of the grid cells in each successive module moving downward could be determined by multiplying the distance between cells in the previous module by a factor of about 1.4, approximately the square root of 2. In the module at the top of the entorhinal cortex, a rat that activated a grid cell at one vertex of a hexagon would have to travel 30 to 35 centimeters to an adjoining vertex. In the next module down, the animal would have to travel 42 to 49 centimeters, and so on. In the lowest module, the distance extended up to several meters in length.

We were extremely excited by the grid cells and their tidy organization. In most parts of the cortex, the neurons have firing patterns that appear chaotic and inaccessible, but here, deep in the cortex, there was a system of cells that fired in a predictable and orderly pattern. We were eager to investigate. But these cells and place cells were not the only ones involved in mapping the mammal's world—other surprises also awaited us.

Back in the mid-1980s and early 1990s, James B. Ranck of SUNY Downstate Medical Center and Jeffrey S. Taube, now at Dartmouth College, had described cells that fired when a rodent faced a particular direction. Ranck and Taube had discovered such head-direction cells in the presubiculum, another region of the cortex adjacent to the hippocampus.

Our studies found that these cells were also present in the entorhinal cortex, intermingled among grid cells. Many head-direction cells in the entorhinal cortex also functioned as grid cells: the locations in the enclosure where they fired also formed a grid, but the cells became active at those locales only when the rat was facing a certain direction. These cells appeared to provide a compass for the animal; by monitoring the cells, one could read out the direction the animal was facing at any given time relative to the surrounding environment.

A few years later, in 2008, we made a discovery in the entorhinal cortex of another cell type. These border cells fired whenever the animal approached a wall or an edge of the enclosure or some other divide. These cells appeared to calculate how far

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the animal was from a boundary. This information could then be used by grid cells to estimate how far the animal had traveled from the wall, and it could also be established as a reference point to remind the rat of the wall's whereabouts at a later time.

Finally, in 2015, yet a fourth kind of cell entered the scene. It responded specifically to the running speed, regardless of the animal's location or direction. The firing rates of these neurons increased in proportion to the speed of movement. Indeed, we could ascertain how fast an animal was moving at a given moment by looking at the firing rates of just a handful of speed cells. In conjunction with head-direction cells, speed cells may serve the role of providing grid cells with continually updated information about the animal's movement—its speed, direction and the distance from where it started.

FROM GRID TO PLACE CELLS

OUR DISCOVERY of grid cells grew out of our desire to uncover the inputs that allow place cells to give mammals an internal picture of their environment. We now understand that place cells integrate the signals from various types of cells in the entorhinal cortex as the brain attempts to track the route an animal has traveled and where it is going in its environment. Yet even these processes do not tell the whole story of how mammals navigate.

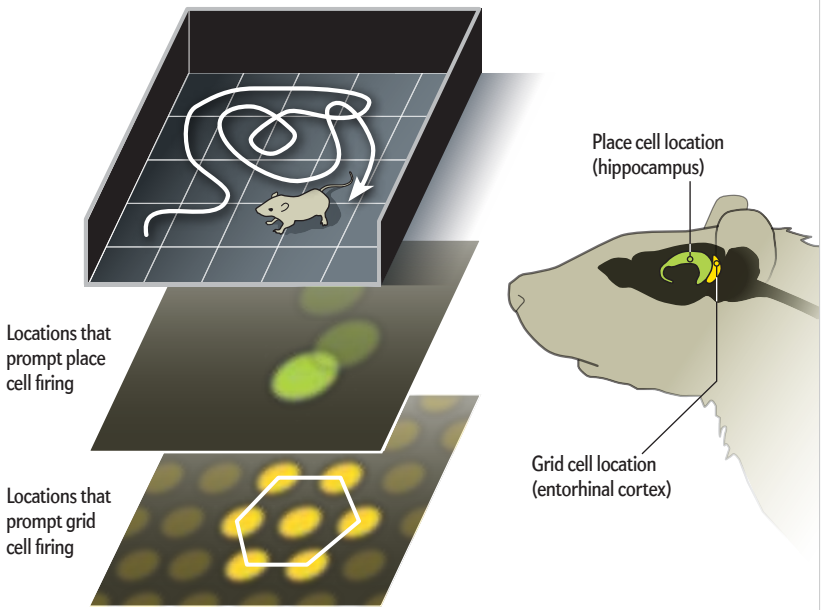
Our initial work focused on the medial (inner) entorhinal cortex. Place cells may also receive signals from the lateral entorhinal cortex, which relays processed input from a number of sensory systems, including information about odor and identity of objects. By integrating inputs from the medial and lateral parts of the entorhinal cortex, place cells interpret signals from throughout the brain. The complex interaction of messages arriving in the hippocampus and the formation of location-specific memories that this enables are still being investigated by our lab and others, and this research will undoubtedly continue for many years to come.

One way to begin to understand how the spatial maps of the medial entorhinal cortex and the hippocampus combine to aid navigation is to ask how the maps differ. John Kubie and the late Robert U. Muller, both at SUNY Downstate Medical Center, showed in the 1980s that maps in the hippocampus made up of place cells may change entirely when an animal moves to a new environment—even to a different colored enclosure at the same location in the same room.

NEUROCARTOGRAPHY

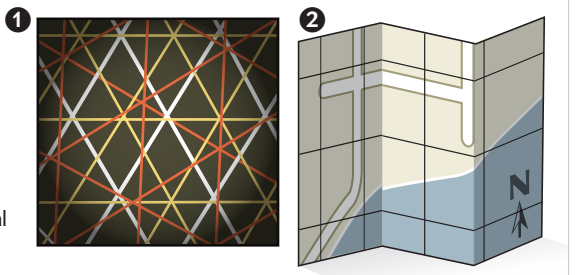
How the Brain Takes Its Bearings

The idea that the brains of mammals make a mental map that mirrors the spatial geometry of the outer world first emerged around 1930. Neuroscientists have subsequently identified cells that work together to create such maps. A key development came in 1971, when an American-British researcher found that place cells in the rat hippocampus fire at particular locations on the willy-nilly path an animal travels. In 2005 the authors discovered grid cells that let an animal measure its location in its environment—say, in relation to the walls of an enclosure. As the animal moves about, each grid cell fires at multiple locations that correspond to the vertices of a hexagon.



A Cognitive Map Emerges

Firing of grid cells produces a map (*1*), akin to a geographical map (*2*). Together with place cells that identify the animal's location in a particular environment, grid cells enable the animal to build a mental picture of its surroundings.



Experiments performed in our own lab, with rats foraging in up to 11 enclosures in a series of different rooms, have shown that each room, in fact, rapidly gives rise to its own independent map, further supporting the idea that the hippocampus forms spatial maps tailored to specific environments.

In contrast, the maps in the medial entorhinal cortex are universal. Grid cells—and head-direction and border cells—that fire together at a particular set of locations on the grid map for one environment also fire at analogous positions on the map for another environment—as if latitude and longitude lines from the first map were imposed on the new setting. The sequence of cells that fire as the animal moves northeast in one room of the cage repeats when the rat goes in that same direction in the other room. The pattern of signaling among these cells in the ento-

SOURCE: "SCIENTIFIC BACKGROUND: THE BRAIN'S NAVIGATIONAL PLACE AND GRID CELL SYSTEM," BY OLE KIEHN AND HANS FORSSBERG, WITH ILLUSTRATIONS BY MATTIAS KARLÉN. NOBELPRIZE.ORG, NOBEL MEDIA AB, 2014 *www.nobelprize.org/nobel_prizes/medicine/laureates/2014/advanced.html (top)*

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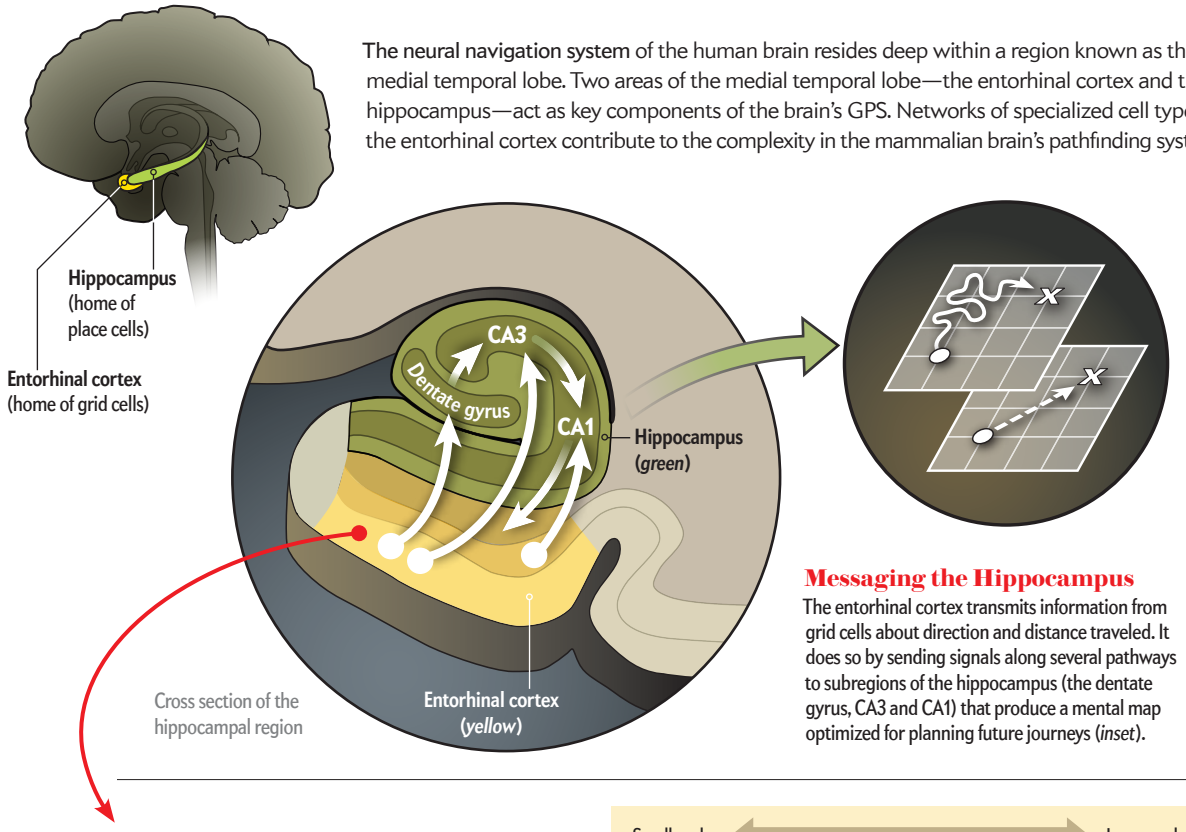
A PARTS LIST

Inside the Brain's GPS

The neural navigation system of the human brain resides deep within a region known as the medial temporal lobe. Two areas of the medial temporal lobe—the entorhinal cortex and the hippocampus—act as key components of the brain's GPS. Networks of specialized cell types in the entorhinal cortex contribute to the complexity in the mammalian brain's pathfinding system.

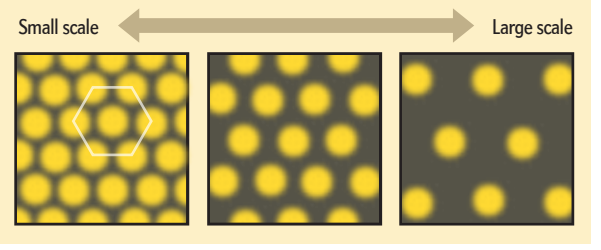


Messaging the Hippocampus

The entorhinal cortex transmits information from grid cells about direction and distance traveled. It does so by sending signals along several pathways to subregions of the hippocampus (the dentate gyrus, CA3 and CA1) that produce a mental map optimized for planning future journeys (*inset*).

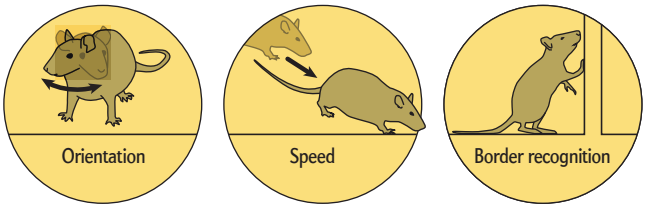
A Close Look at Grid Cell Organization …

… reveals that the spacing of the hexagonal elements that aid in creating a spatial map change when moving from top to bottom in the entorhinal cortex. The broader spacings correspond to larger distances the rat needs to travel to activate a vertex on the grid. At the top of the entorhinal cortex, a rat that activates a grid cell at one vertex of a hexagon will have to move 30 to 35 centimeters to an adjoining vertex. At the bottom, the animal needs to go as far as several meters.



Other Specialized Cells Recently Discovered …

… in the entorhinal cortex of rodents convey information to the hippocampus about the orientation of an individual's head, its speed of movement, and the distance to walls and other obstacles encountered. The output of these cells is combined to help create a composite map of the animal's environs.



MYSTERIES OF THE MIND

rhinal cortex is what the brain uses for navigating through its surroundings.

These codes are then transmitted from the entorhinal cortex to the hippocampus, where they are used to form maps specific to a particular place. From the standpoint of evolution, two sets of maps that integrate their information to guide animals appear to be an efficient solution for a system used by animals for spatial navigation. The grids formed in the medial entorhinal cortex that measure distance and direction do not change from one room to the next. In contrast, the place cells of the hippocampus form individual maps for every single room.

LOCAL MAPS

UNDERSTANDING the neural navigation system remains a work in progress. Almost all our knowledge of place and grid cells has been obtained in experiments in which electrical activity from neurons is recorded when rats or mice walk about randomly in highly artificial environments—boxes with flat

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bottoms and no internal structures to serve as landmarks.

A lab differs substantially from natural environments, which change constantly and are full of three-dimensional objects. The reductionism of the studies raises questions about whether place cells and grid cells fire in the same way when animals find themselves outside the lab.

Experiments in complex mazes that try to mimic animals' natural habitat provide a few clues to what might be going on. In 2009 we recorded grid cells as animals moved through an intricate maze in which they encountered a hairpin turn at the end of each alley that marked the beginning of the next passageway. The study showed that, as expected, grid cells formed patterns of hexagons to map out distances for the rats in individual alleys of the maze. But each time an animal turned from one alley to the next, an abrupt transition occurred. A separate grid pattern was then superimposed on the new alley, almost as if the rat were entering an entirely different room.

Later work in our lab has shown that grid maps also fragment into smaller maps in open environments if these spaces are large enough. We are now researching how these smaller maps merge to form an integrated map of a given area. Even these experiments are oversimplified because the enclosures are flat and horizontal. Experiments performed in other labs—observing flying bats and rats that climb around in cages—are beginning to offer some clues: place cells and head-direction cells seem to fire in specific places throughout any three-dimensional space, and most likely grid cells do as well.

SPACE AND MEMORY

THE NAVIGATIONAL SYSTEM in the hippocampus does more than help animals get from point A to point B. Beyond receiving information about position, distance and direction from the medial entorhinal cortex, the hippocampus makes a record of what is located in a particular place—whether a car or a flagpole—as well as the events that take place there. The map of space created by place cells thus contains not only information about an animal's whereabouts but also details about the animal's experiences, similar to Tolman's conception of a cognitive map.

Some of this added information appears to come from neurons in the lateral part of the entorhinal cortex. Particulars about objects and events fuse with an animal's coordinates and are laid down as a memory. When the memory is later retrieved, both the event and the position are called to mind.

This coupling of place with memory recalls a strategy for memorization invented by the ancient Greeks and Romans. The "method of loci" lets a person memorize a list of items by imagining putting each item at a position along a well-known path through a place, say, a landscape or a building—an arrangement often called a memory palace. Participants in memory contests still use the technique to recall long lists of numbers, letters or playing cards.

Sadly, the entorhinal cortex is among the first areas to fail in people with Alzheimer's disease. The illness causes brain cells there to die, and a reduction in its size is considered a reliable measure for identifying at-risk individuals. The tendency to wander and get lost is also among the earliest indicators of the disorder. In the later stages of Alzheimer's, cells die in the hippocampus, producing an inability to recall experiences or remember concepts such as the names of colors. In fact, a recent study has provided evidence that young individuals with a gene that places them at an elevated risk for Alzheimer's may have deficiencies in the functioning of their grid cell networks—a finding that may lead to new ways of diagnosing the disease.

A RICH REPERTOIRE

TODAY, MORE THAN 80 YEARS since Tolman first proposed the existence of a mental map of our surroundings, it is clear that place cells are just one component of an intricate representation the brain makes of its spatial environment to calculate location, distance, speed and direction. The multiple cell types that have been found in the navigation system of the rodent brain also occur in bats, monkeys and humans. Their existence across mammalian taxonomic orders suggests that grid and other cells involved in navigation arose early in the evolution of mammals and that similar neural algorithms are used to compute position across species.

Many of the building blocks of Tolman's map have been discovered, and we are beginning to understand how the brain creates and deploys them. The spatial representation system has become one of the best-understood circuits of the mammalian cortex, and the algorithms that it uses are starting to be identified to help unlock the neural codes the brain uses for navigation.

As with so many other areas of inquiry, new findings raise new questions. We know that the brain has an internal map, but we still need a better understanding of how the elements of the map work together to produce a cohesive representation of positioning and how the information is read by other brain systems to make decisions about where to go and how to get there.

Other questions abound. Is the spatial network of the hippocampus and the entorhinal cortex limited to navigation of local space? In rodents, we examine areas that have radii of only a few meters. Are place and grid cells also used for long-distance navigation, such as when bats migrate hundreds or thousands of kilometers?

Finally, we wonder how grid cells originate, whether there is a critical formative period for them in an animal's development and whether place and grid cells can be found in other vertebrates or invertebrates. If invertebrates use them, the finding would imply that evolution has used this spatial-mapping system for hundreds of millions of years. The brain's GPS will continue to provide a rich trove of leads for new research that will occupy generations of scientists in the decades ahead. SA

May-Britt Moser and **Edvard I. Moser** are professors in psychology and neuroscience at the Norwegian University of Science and Technology in Trondheim. The two co-founded the Kavli Institute for Systems Neuroscience in 2007 and the Center for Neural Computation in 2013, both located at the university. In 2014 they shared the Nobel Prize in Physiology or Medicine with John O'Keefe of University College London for the discovery of the brain's positioning system.

MORE TO EXPLORE

Grid Cells and the Entorhinal Map of Space. Edvard I. Moser. Nobel lecture, December 7, 2014. www.nobelprize.org/nobel_prizes/medicine/laureates/2014/edvard-moser-lecture.html

Grid Cells, Place Cells and Memory. May-Britt Moser. Nobel lecture, December 7, 2014. www.nobelprize.org/nobel_prizes/medicine/laureates/2014/may-britt-moser-lecture.html

Ten Years of Grid Cells. D. C. Rowland et al. in *Annual Reviews of Neuroscience,* Vol. 39, pages 19–40; July 8, 2016.

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Uncanny Sight in the BLIND

Some people who are blind because of brain damage have "blindsight": an extraordinary ability to react to emotions on faces and even navigate around obstacles

By Beatrice de Gelder

THE VIDEO MY COLLEAGUES AND I SHOT is amazing. A blind man is making his way down a long corridor strewn with boxes, chairs and other office paraphernalia. The man, known to the medical world as TN, has no idea the obstacles are there. And yet he avoids them all, here sidling carefully between a wastepaper basket and the wall, there going around a camera tripod, all without knowing he has made any special maneuvers. TN may be blind, but he has "blindsight"—the remarkable ability to respond to what his eyes can detect without knowing he can see anything at all.

IN BRIEF

Some people who are blind because of brain damage exhibit "blindsight," a phenomenon where they respond to objects and images they cannot consciously see.
Blindsight can detect many visual features, including colors, motion, simple shapes, and the emotion expressed by a person's face or posture.
Researchers are mapping the evolutionarily ancient brain areas responsible for blindsight and exploring the limits of this remarkable ability.

DARREN BRAUN

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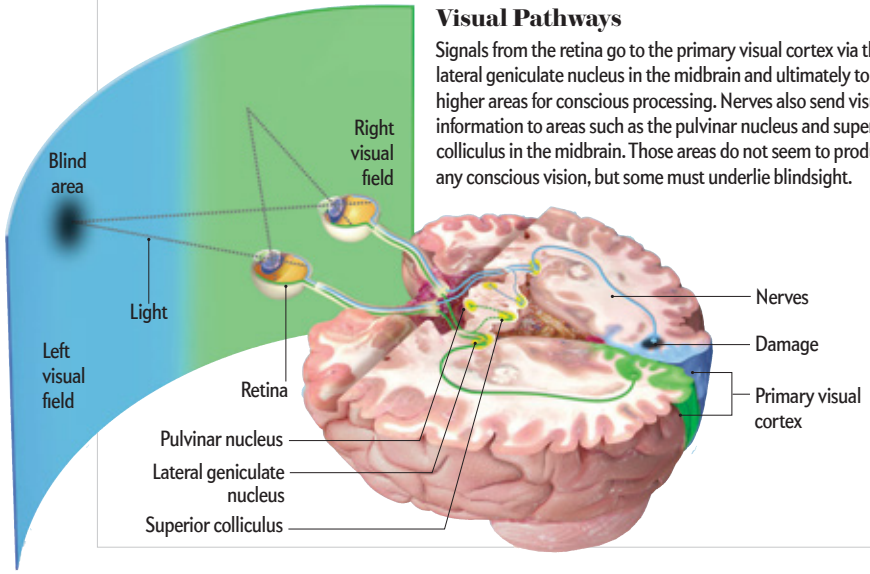
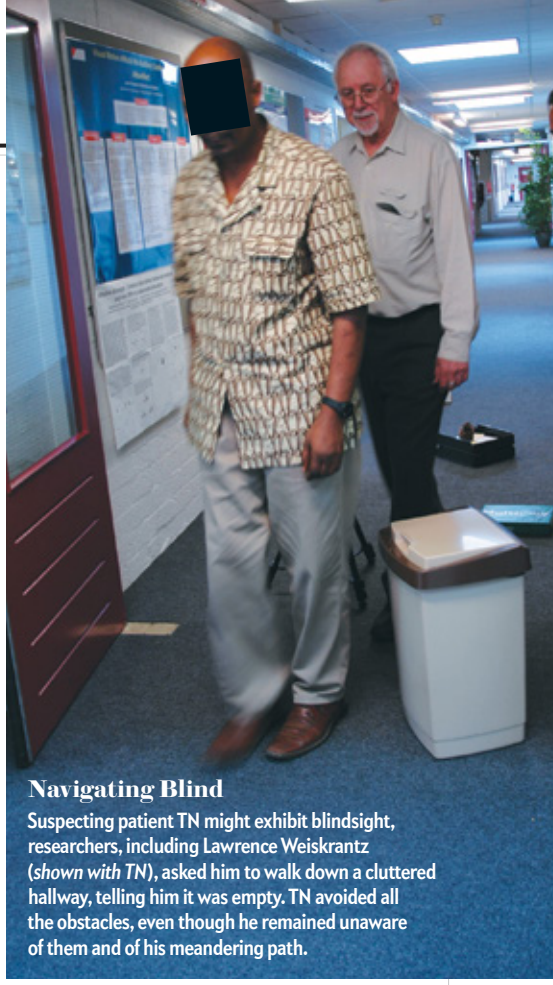
What Is Blindsight?

Conscious vision in humans depends on the integrity of a region of the brain called the primary visual cortex. Damage there causes blindness in corresponding areas of the visual field. "Blindsight" occurs when patients respond in some way to an item displayed in their blind area, where they cannot consciously see it. In a dramatic demonstration of the phenomenon, a patient called TN navigated an obstacle course despite his total blindness.



Visual Pathways

Signals from the retina go to the primary visual cortex via the lateral geniculate nucleus in the midbrain and ultimately to higher areas for conscious processing. Nerves also send visual information to areas such as the pulvinar nucleus and superior colliculus in the midbrain. Those areas do not seem to produce any conscious vision, but some must underlie blindsight.



Navigating Blind

Suspecting patient TN might exhibit blindsight, researchers, including Lawrence Weiskrantz (*shown with TN*), asked him to walk down a cluttered hallway, telling him it was empty. TN avoided all the obstacles, even though he remained unaware of them and of his meandering path.

TN's blindness is of an extremely rare type, caused by two strokes he suffered in 2003. The strokes injured an area at the back of his brain called the primary visual cortex, first on his left hemisphere and five weeks later on the right. His eyes remained perfectly healthy, but with his visual cortex no longer receiving the incoming signals he became completely blind.

This study of TN navigating along the hallway is probably the most dramatic demonstration of blindsight ever reported. Other patients who have lost vision because of damage to the primary visual cortex have exhibited less spectacular but equally mysterious cases of the phenomenon—responding to things they cannot consciously see, ranging from simple geometric shapes to the complex image of a person's face expressing an emotion. Scientists have also induced a similar effect in healthy people, by temporarily "switching off" their visual cortex or by outfoxing it in other ways.

Today research into blindsight seeks to understand the range of perceptual abilities that may be retained by the cortically blind and to determine which brain regions and neuronal pathways are responsible. The knowledge being gained says something about us all because even if we never suffer a catastrophic injury resembling TN's, the same unconscious brain functions manifest in him as the astonishing ability to see without knowing are surely a constant, invisible part of our own daily existence.

A CONTROVERSIAL HISTORY

AS LONG AGO AS 1917, doctors reported cases like blindsight—then called residual vision—in soldiers injured in World War I. Half a century would pass, however, before more organized and objective research into the capacity began. First, Lawrence Weiskrantz and his student Nicholas K. Humphrey, both then at the University of Cambridge, studied surgically altered monkeys in 1967. Then, in 1973, Ernst Pöppel, the late Richard Held and Douglas Frost, all then at the Massachusetts Institute of Technology, measured the eye movements of a patient and found he had a slight tendency to look toward stimuli that he did not report he could see.

These discoveries spurred further systematic investigations of animals lacking the primary visual cortex (also called V1), most of them conducted by Weiskrantz and his collaborators. A number of studies established that animals retain significant visual abilities after removal of their visual cortex (for example, detecting movement and discriminating shapes).

Weiskrantz and his co-workers also began studies in 1973 with a person known as DB who had recently lost part of his visual cortex in surgery to remove a tumor. The wider research community, however, initially greeted reports of human blindsight with great skepticism.

Blindsight seems counterintuitive, if not outright contradictory. After all, how could people see without knowing that they see? Just as it does not make sense to say that I am in pain but do not know it, it also does not make sense, on the face of it, to suggest that somebody can see something when he insists he is blind.

The relation between seeing and knowing is more complicated than we commonly assume. For instance, people with normal sight have a blind spot, although we are not usually aware of this hole in our sight or handicapped by it.

Another reason for disbelief was the paucity of human evi-

KEITH KASNOT (*illustration*); BEATRICE DE GELDER (*photograph*)

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dence: subjects with cortical blindness who can be studied are rare. The primary visual cortex is only a few centimeters across in adults, and brain damage is seldom restricted to just that area, knocking out the patient's vision yet leaving other faculties intact enough for meaningful research on what the brain continues to perceive. Even so, it is now clear that many more patients with damage to the visual cortex have blindsight than scientists realized in the past, and skepticism has abated.

Most of these patients still have some functioning in the primary visual cortex. Many have damage to only a small part of V1, leading to a small island of blindness in their visual field; others lose the entire left or right half of V1, leaving them blind across the corresponding (opposite) half of their visual field. Blindsight in these cases involves detecting objects or images presented in the blind area, where the patient cannot see them consciously.

Traditional methods for studying vision in humans have relied on the viewers' verbal reports of what they perceive. Tested in that way, subjects will report not seeing anything in the blind part of their visual field. More indirect methods, however, can reveal that these unseen visual stimuli actually do influence how a patient responds.

In some experiments, patients show clear physiological changes, such as constriction of the pupil, as signs of unconscious seeing. And subjects can react differently to items shown in the intact visual field depending on what is presented at the same time in the blind field. When asked to guess which of several alternative items are displayed in the blind field, a patient may answer correctly almost every time.

Another important experimental tool is neuroimaging, which can provide direct evidence about the brain regions involved in blindsight and the pathways that the visual information travels. Brain imaging has been instrumental in dispelling lingering suspicions that some spared pieces of cortex might explain residual vision.

Collectively, these various kinds of experiments have revealed that people can unconsciously detect a wide range of visual attributes, including color, simple shapes such as X and O, simple direction of motion. Large shapes, as well as very fine detail, seem hard to detect. For instance, patients detect features of a grating most effectively if its lines are comparable to venetian blinds viewed from about 1.5 to 4.5 meters (five to 15 feet).

We were inspired to try the navigation experiment with TN by research Weiskrantz and Humphrey did in the 1970s: a monkey with no primary visual cortex freely moved around a room cluttered with objects without bumping into any of them. Nevertheless, we were amazed when TN made his way along the hallway with no collisions at all. Personalized psychophysical tests to assess his conscious vision had not found any visual functioning, including detection of big targets.

TN's ability to move down the corridor was reminiscent of sleepwalking, another phenomenon in which people exhibit a capacity to perform in some way without having any awareness of their actions. Indeed, when we questioned him afterward, he insisted he had simply walked along the hallway: he was not only unaware of seeing anything but also oblivious to how he had maneuvered around the unseen objects. He was at a loss to explain or even to describe his actions.

SIGHTLINES

What Can Be Detected?

Blindsight is strongest when visual details are about the size of a quarter viewed from five to 15 feet away. It can detect an assortment of basic visual properties, including:

- Simple shapes
- Arrays of lines
- Objects appearing or disappearing
- Movement
- Color
- Orientation of lines

BLINDSIGHT can also recognize emotions being expressed by a person, but not who the person is or what the person's gender is.

BLINDSIGHT FOR EMOTIONS

MOVING AROUND is one of the most fundamental tasks an animal faces, so perhaps it should not be surprising that the brain has ways to support navigation even when the primary visual cortex and conscious vision are hobbled. As a social species, humans also depend for their survival on successful communication with others. They must recognize other people, along with their gestures and signs of what they are thinking. With such thoughts in mind, my collaborators and I began to wonder in the late 1990s if people with cortical damage could detect visual displays such as the emotion on a face or the meaning of a body posture in the usually inaccessible parts of their visual field.

In 1999 we started conducting tests using movies of faces. Vision researchers generally consider faces to be visually complex—far more difficult to process than gratings and other elementary shapes—but a face is a very natural object for the human brain to handle. Our patient, GY, had lost all of his primary visual cortex on the left side in childhood, rendering him blind on the right side of his visual field. We found he could reliably guess the expression appearing on faces he did not consciously perceive, but he seemed truly blind to a variety of nonemotional facial attributes such as personal identity.

To study blindsight of emotions further, in 2009 we exploited a phenomenon called emotional contagion, a tendency to match one's own facial expressions to those of others that we see. Researchers measure emotional contagion with a procedure called facial electromyography, by which electrodes on a subject's face re-

ANTHONY MARSLAND *Getty Images (happy)*: GETTY IMAGES *(sad)*

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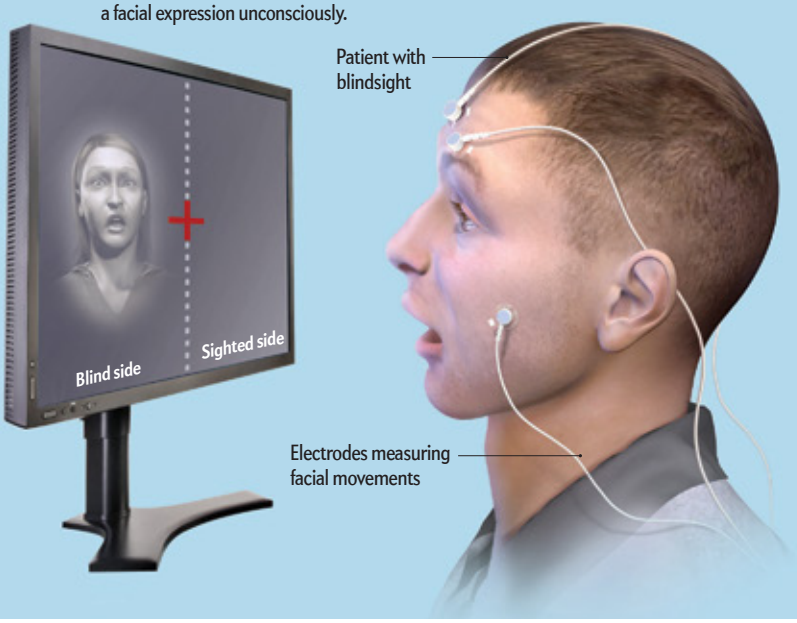
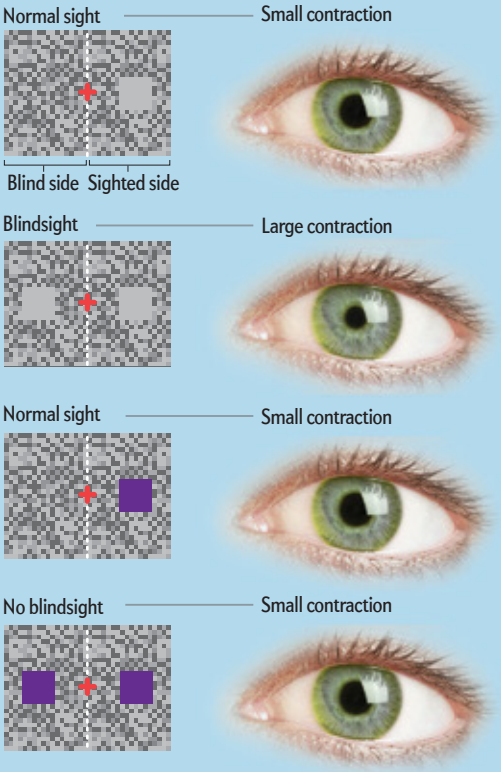
Investigating Blindsight

Because total cortical blindness like patient TN's is rare, studies of blindsight often use patients blind on one side of their visual field. The patient stares at a fixed point while images are presented on each side. The subject may be asked to "guess" what is on the blind side or to press a button on seeing items on the sighted side. Equipment may monitor brain activity and measure involuntary responses such as tiny facial movements and pupil dilation.

Does Blindsight See Emotions?

Patients shown images on their blind side of people expressing emotions correctly guessed the emotion most of the time. Facial muscles used in smiling and frowning reacted in ways that matched the kind of emotion in the unseen image (*below, exaggerated*). Thus, the emotions were recognized without involving conscious sight. The effect worked with images of faceless bodies as well as faces, implying that patients were recognizing an emotion and not merely mimicking a facial expression unconsciously.





What Brain Areas Does Blindsight Use?

Researchers showed patients gray and purple squares, knowing the superior colliculus region in the midbrain receives no signals from the retina about purple objects. Gray squares but not purple ones triggered signs of blindsight such as greater pupil contractions. These results, along with neuroimaging of the patients in action, imply that the superior colliculus plays a critical role in blindsight.

cord nerve signals going to muscles involved in smiling or frowning. We used this technique on GY and DB while showing them still images of faces and whole bodies expressing happiness or fear.

All the stimuli triggered emotional reactions as measured by electromyography, irrespective of whether the image was on the patient's sighted side or his blind side. In fact, surprisingly, the unseen images produced a faster response than those seen consciously. We also monitored pupil dilations, a measure of physiological arousal. The unseen fearful images produced the strongest effect—seemingly the more we are consciously aware of an emotional signal, the slower and weaker is our reaction.

One school of thought holds that emotional contagion arises because people unconsciously mimic the expressions they see, without necessarily recognizing the emotion itself. But because our patients reacted not only to faces but also to bodies (which had blurred faces), we concluded that they are reacting to the emotions observed.

BLINDSIGHT FOR ALL

BECAUSE THE NUMBER of suitable patients for blindsight studies is extremely small, inducing the phenomenon temporarily in people with completely healthy brains is a valuable tool for controlled experiments. One technique uses visual "masking," more popularly known as the use of subliminal images: a visual stimulus flashes before the experimental subject very briefly, followed immediately by a pattern in the same location. The pattern interferes with conscious processing of the fleeting subliminal image, leaving the subject with no conscious awareness of seeing it, but experiments can tease out objective evidence that it was seen. Other experiments temporarily disable the visual cortex by applying magnetic fields to the back of the head, a technique called transcranial magnetic stimulation.

Numerous studies have shown that healthy subjects can reliably "guess" the nature of a stimulus even when it is presented too briefly for them to perceive it consciously or when transcranial magnetic stimulation is disabling their visual cortex. Much research has also investigated how normally sighted observers react to emotional stimuli they cannot see consciously. Even before such blindsight experiments got under way, studies in animals and humans suggested that structures in the subcortex (areas of the brain that are deeper and more evolutionarily ancient than the cortex) can initiate appropriate responses before areas such as the visual cortex have analyzed the stimulus in detail. This nonconscious system seems to operate in parallel with the normal, predominantly cortical, processing routes. These sub-

KEITH KASNOT (*experiment and eyes*); LUCY READING-IKKANDA (*squares*)

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cortical areas that are activated by subliminal emotional stimuli are the leading suspects in processing emotions detected by blindsight in permanently cortically blind patients.

Yet scientists continue to debate whether similar forms of temporary blindness induced in normally sighted people are the functional equivalent of blindsight in patients with permanent cortical damage. In particular, visual-masking techniques, such as the use of subliminal images, permit the visual cortex to process information as usual but interfere with further conscious processing. Consequently, "blindsight" of subliminal images could be a quite distinct phenomenon from blindsight in patients, involving its own characteristic network of brain regions. Transcranial magnetic stimulation presumably mimics cortical damage closely, but to know whether the resulting blindsight actually involves the same neuronal pathways requires experiments that combine the technique with neuroimaging.

Conversely, after an injury, a patient's brain (even an adult's) may start rewiring itself to compensate for the loss. Such neural plasticity could well create pathways for blindsight that are not present in the normally sighted people who are studied using transcranial magnetic stimulation and visual masking. Until these issues are better understood, studies of patients with injuries will remain crucial for fathoming how noncortical regions produce residual vision.

Mapping Neural Pathways

Researchers are using advanced imaging techniques to attempt to trace the neural pathways that visual information travels in the brain to produce blindsight.

One such method is a kind of magnetic resonance imaging called diffusion tensor imaging, which relies on water diffusing more rapidly along neurons than across them.

Diffusion tensor imaging has mapped bundles of neurons that may be responsible for blindsight of emotions. The pathway connects the pulvinar nucleus and superior colliculus to the amygdala, which plays a key role in processing emotions.

NAVIGATION MINDSET

RESEARCH HAS NOT YET fully determined the neural structures responsible for blindsight in the cortically blind, but the most likely candidate to play a central role is a brain region called the superior colliculus (SC), which sits in a part of the subcortex called the midbrain. In nonmammals such as birds and fish, the SC is the main structure receiving input from the eyes. In mammals it is overshadowed by the visual cortex but remains involved in controlling eye movements, among other visual functions. Blindsight would exploit information that travels from the retina to the SC without first going through the primary visual cortex.

In a recent study, we showed that this midbrain area is essential for translating a visual signal that cannot be consciously perceived into an action. Specifically, we had a patient press a button whenever we showed him a square on his sighted side. Sometimes we simultaneously presented a square on his blind side. Sometimes we used gray squares and sometimes purple ones. We chose a purple hue that only one type of light-detecting cone cell in the retina detects, knowing that the SC receives no inputs from that type; it is blind to this purple.

A gray square on our patient's blind side accelerated his response and made his pupils constrict more—a sign of processing the stimulus—whereas a purple square had neither effect. In other words, he exhibited blindsight of gray stimuli but not purple ones. Brain scans showed that his SC was most strongly activated only by the gray stimulus on his blind side. Some other areas in the midbrain have been suspected of being involved in blindsight instead of the SC, but in our experiment their activity seemed unrelated to the occurrence of blindsight.

These findings show that the SC acts in the human brain as an interface between sensory processing (sight) and motor processing (leading to the patient's action), thereby contributing to visually guided behavior in a way that is apparently separate from the pathways involving the cortex and entirely outside conscious visual experience.

Blindsight has captured a lot of attention from philosophers, who are intrigued by the paradoxical idea of seeing without knowing that one sees. The idea, of course, is only a paradox if "seeing" is always taken to mean "consciously seeing." That mindset was a stumbling block to acceptance of blindsight by scientists, delaying progress in understanding the role of unconscious seeing in human cognition.

It can also be a stumbling block for patients suffering from cortex-based loss of vision, preventing them from unlocking the potential of their residual visual skills in their everyday lives. For example, TN views himself as a blind person, and he will remain totally dependent on his white cane until he is convinced he can see without knowing it.

In the years since the original blindsight findings, research has shifted from a concentration on local brain areas to the idea of a whole-brain integrative network. This new perspective is driven by new findings about wide-ranging subcortical and cortical connectivity. Behaviorally and functionally separate networks consist of partly the same nodes, or areas, but sustain different functions and can operate in parallel—for example, object vision (one network) with or without subjective awareness (another network). The existence of nonconscious vision in blindsight and control patients shows that there are limits to our understanding of how these networks are integrated, how they are distinctive and how the brain juggles the various inputs. For blindsight, as with many paradoxical phenomena in science, we are discovering that there is more to it than meets the eye. SA

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MORE TO EXPLORE

Helen, a Blind Monkey Who Sees Everything. Nicholas Humphrey. Video from 1971. Available at https://www.youtube.com/watch?v=rDIsxwQHwt8

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How Babies Think

Even the youngest children know, experience and learn far more than scientists ever thought possible

By Alison Gopnik

IN BRIEF

Babies' and young children's cognitive abilities far surpass those that psychologists long attributed to them. They can, for instance, imagine another person's experiences and grasp cause and effect.

Children learn about the world around them much as scientists do—in effect, conducting experiments, analyzing statistics and forming theories to account for their observations.

The long helplessness of babies may be an evolutionary trade-off, a necessary consequence of having brains wired for prodigious feats of learning and creativity.

Photographs by Timothy Archibald

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THIRTY YEARS AGO MOST PSYCHOLOGISTS, PSYCHIATRISTS AND philosophers thought that babies and young children were irrational, egocentric and amoral. They believed children were locked in the concrete here and now—unable to understand cause and effect, imagine the experiences of other people, or appreciate the difference between reality and fantasy. People still often think of children as defective adults. But in the past three decades scientists have discovered that even the youngest children know more than we would ever have thought possible. Moreover, studies suggest that children learn about the world in much the same way that scientists do—by conducting experiments, analyzing statistics, and forming intuitive theories of the physical, biological and psychological realms. Since about 2000, researchers have started to understand the underlying computational, evolutionary and neurological mechanisms that underpin these remarkable early abilities. These revolutionary findings not only change our ideas about babies, they give us a fresh perspective on human nature itself.

PHYSICS FOR BABIES

WHY WERE WE SO WRONG about babies for so long? If you look cursorily at children who are four years old and younger (the age range I will discuss in this article), you might indeed conclude that not much is going on. Babies, after all, cannot talk. And even preschoolers are not good at reporting what they think. Ask your average three-year-old an open-ended question, and you are likely to get a beautiful but incomprehensible stream-of-consciousness monologue. Earlier researchers, such as the pioneering Swiss psychologist Jean Piaget, concluded that children's thought itself was irrational and illogical, egocentric and "precausal"—with no concept of cause and effect.

The new science that began in the late 1970s depends on techniques that look at what babies and young children do instead of just what they say. Babies look longer at novel or unexpected events than at more predictable ones, and experimenters can use this behavior to figure out what babies expect to happen. The strongest results, however, come from studies that observe actions as well: Which objects do babies reach for or crawl to? How do babies and young children imitate the actions of people around them?

Although very young children have a hard time telling us what they think, we can use language in more subtle ways to tease out what they know. For example, Henry Wellman of the University of Michigan has analyzed recordings of children's spontaneous conversations for clues to their thinking. We can give children very focused questions—for instance, asking them to choose between just two alternatives rather than asking an open-ended question.

In the mid-1980s and through the 1990s, scientists using these techniques discovered that babies already know a great deal about the world around them. That knowledge goes well beyond concrete, here-and-now sensations. Researchers such as Renee Baillargeon of the University of Illinois and Elizabeth S. Spelke of Harvard University found that infants understand fundamental physical relations such as movement trajectories, gravity and containment. They look longer at a toy car appearing to pass through a solid wall than at events that fit basic principles of everyday physics.

By the time they are three or four, children have elementary ideas about biology and a first understanding of growth, inheritance and illness. This early biological understanding reveals that children go beyond superficial perceptual appearances when they reason about objects. Susan A. Gelman, also at Michigan, found that young children believe that animals and plants have an "essence"—an invisible core that stays the same even if outside appearances change.

For babies and young children, the most important knowledge of all is knowledge of other people. Andrew N. Meltzoff of the University of Washington showed that newborns already understand that people are special and will imitate their facial expressions.

In 1996 Betty Repacholi (now at the University of Washington) and I found that 18-month-olds can understand that I might want one thing, whereas you want another. An experimenter showed 14- and 18-month-olds a bowl of raw broccoli and a bowl of goldfish crackers and then tasted some of each, making either a disgusted face or a happy face. Then she put her hand out and asked, "Could you give me some?" The 18-month-olds gave her

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broccoli when she acted as if she liked it, even though they would not choose it for themselves. (The 14-month-olds always gave her crackers.) So even at this very young age, children are not completely egocentric—they can take the perspective of another person, at least in a simple way. By age four, their understanding of everyday psychology is even more refined. They can explain, for instance, if someone is acting oddly because he or she believes something that is not true.

By the end of the 20th century experiments had thus charted impressively abstract and sophisticated knowledge in babies and the equally impressive growth of that knowledge as children get older. Some scientists have argued that babies must be born knowing much of what adults know about how objects and people behave. Undoubtedly, newborns are far from being blank slates, but the changes in children's knowledge also suggest that they are learning about the world from their experiences.

One of the greatest mysteries of psychology and philosophy is how human beings learn about the world from a confusing mess of sensory data. Over the past decade researchers have begun to understand much more about how babies and young children can learn so much so quickly and accurately. In particular, we have discovered that babies and young children have an extraordinary ability to learn from statistical patterns.

BABY MATH

Statistician at Work

Babies are skillful statistical analysts. Experiments showed that eight-month-olds notice if an improbable number of red Ping-Pong balls are taken out of a collection that is mostly white. Variations of the experiments (such as swapping the role of red and white) control against alternative explanations (such as having a greater interest in red objects). Twenty-month-olds tested with green and yellow toys inferred that a person taking an unusually large number of the rare color would prefer to be given a toy of that color. Thus, babies and young children learn about the world like scientists—by detecting statistical patterns and drawing conclusions from them.

THE STATISTICS OF BLICKETS

IN 1996 JENNY R. SAFFRAN, Richard N. Aslin and Elissa L. Newport, all then at the University of Rochester, first demonstrated this ability in studies of the sound patterns of language. They played sequences of syllables with statistical regularities to some eight-month-old babies. For example, "ro" might follow "bi" only one third of the time, whereas "da" might always follow "bi." Then they played the babies new strings of sounds that either followed these patterns or broke them. Babies listened longer to the statistically unusual strings. More recent studies show that babies can detect statistical patterns of musical tones and visual scenes, as well as more abstract grammatical patterns.

Babies can even understand the relation between a statistical sample and a population. In a 2008 study my University of California, Berkeley, colleague Fei Xu showed eight-month-old babies a box full of mixed-up Ping-Pong balls: say, 80 percent white and 20 percent red. The experimenter would then take out five balls, seemingly at random. The babies were more surprised (that is, they looked longer and more intently at the scene) when Xu pulled four red balls and one white one out of the box—an improbable outcome—than when she pulled out four white balls and one red one.

Detecting statistical patterns is just the first step in scientific discovery. Even more impressively, children (like scientists) use those statistics to draw conclusions about the world. In a version of the Ping-Pong ball study with 20-month-old babies using toy green frogs and yellow ducks, the experimenter would take five toys from the box and then ask the child to give her a toy from some that were on the table. The children showed no preference between the colors if the experimenter had taken mostly green frogs from the box of mostly green toys. Yet they specifically gave her a duck if she had taken mostly ducks from the box—apparently the children thought her statistically unlikely selection meant that she was not acting randomly and that she must prefer ducks.

In my laboratory we have been investigating how young children use statistical evidence and experimentation to figure out cause and effect, and we find their thinking is far from being "precausal." We introduce them to a device we call "the blicket detector," a machine that lights up and plays music when you put some things on it but not others. Then we can give children patterns of evidence about the detector and see what causal conclusions they draw. Which objects are the blickets?

In 2007 Tamar Kushnir, now at Cornell University, and I found that preschoolers can use probabilities to learn how the machine works. We repeatedly put one of two blocks on the machine. The machine lit up two out of three times with the yellow block but only two out of six times for the blue one. Then we gave the children the blocks and asked them to light up the machine. These children, who could not yet add or subtract, were more likely to put the high-probability yellow block on the machine. (More recently, Anna Waismeyer of the University of Washington and I discovered that even 24-month-olds could do this.)

They still chose correctly when we waved the high-probability block over the machine, activating it without touching it. Although they thought this kind of "action at a distance" was unlikely at the start of the experiment (we asked them), these children could use probability to discover brand-new and surprising facts about the world.

In another experiment Laura Schulz, now at the Massachusetts Institute of Technology, and I showed four-year-olds a toy with a switch and two gears, one blue and one yellow, on top. The gears turn when you flip the switch. This simple toy can work in many ways. Perhaps the switch makes both gears turn at once, or perhaps the switch turns the yellow gear, which turns the blue one, and so on. We showed the children pictures illustrating each of these possibilities—the yellow gear would be depicted push-

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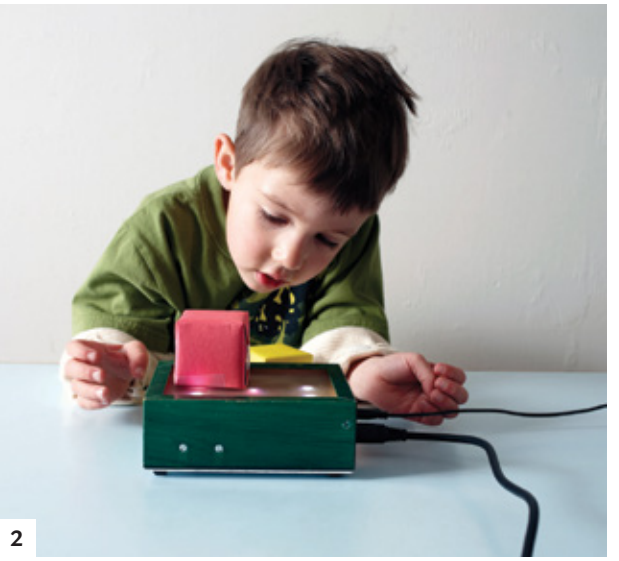
Natural Experimenters

Four-year-olds are adept at interpreting evidence to learn about cause and effect, such as determining if one cog on a machine is turning another (*1*). Some even carried out the correct experiments (and drew the right conclusion) while freely "playing" with the toy. Research involving a "blicket detector" (*2*), which is more likely to light up for some combinations of blocks than for others, found that four-year-olds could use statistics to learn how the machine worked, even when it showed new, unexpected behavior. Indeed, they were more open-minded than adults when faced with evidence that the machine responded to blocks in an unusual way.

1



2

ing the blue one, for instance. Then we showed them toys that worked in one or the other of these ways and gave them rather complex evidence about how each toy worked. For example, the children who got the "causal chain toy" saw that if you removed the blue gear and turned the switch, the yellow gear would still turn but that if you removed the yellow gear and turned the switch, nothing happened.

We asked the children to pick the picture that matched how the toy worked. Four-year-olds were amazingly good at ascertaining how the toy worked based on the pattern of evidence that we presented to them. Moreover, when other children were just left alone with the machine, they played with the gears in ways that helped them learn how it worked—as if they were experimenting.

Another study by Schulz used a toy that had two levers and a duck and a puppet that popped up. One group of preschoolers was shown that the duck appeared when you pressed one lever and that the puppet popped up when you pressed the other one. The second group saw that when you pressed both levers at once, both toys popped up, but they never got a chance to see what the levers did separately. Then the experimenter had the children play with the toy. Children from the first group played with the toy much less than those from the second group. They already knew how it worked and were less interested in exploring it. The second group faced a mystery, and they spontaneously played with the toy, soon uncovering which lever did what.

These studies suggested that when children play spontaneously ("getting into everything") they are also exploring cause and effect and doing experiments—the most effective way to discover how the world works.

THE BABY COMPUTER

OBVIOUSLY CHILDREN are not doing experiments or analyzing statistics in the self-conscious way that adult scientists do. The children's brains, however, must be unconsciously processing information in a way that parallels the methods of scientific discovery. The central idea of cognitive science is that the brain is a kind of computer designed by evolution and programmed by experience.

Computer scientists and philosophers have begun to use mathematical ideas about probability to understand the powerful learning abilities of scientists—and children. A whole new approach to developing computer programs for machine learning uses what are called probabilistic models, also known as Bayesian models or Bayes nets. The programs can unravel complex gene-expression problems or help understand climate change. The approach has also led to new ideas about how the computers in children's heads might work.

Probabilistic models combine two basic ideas. First, they use mathematics to describe the hypotheses that children might have about things, people or words. For example, we can represent a child's causal knowledge as a map of the causal relations between events. An arrow could point from "press blue lever" to "duck pops up" to represent that hypothesis.

Second, the programs systematically relate the hypotheses to the probability of different patterns of events—the kind of pat-

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terns that emerge from experimentation and statistical analysis in science. Hypotheses that better fit the data become more likely. I have argued that children's brains may relate hypotheses about the world to patterns of probability in a similar way. Children reason in complex and subtle ways that cannot be explained by simple associations or rules.

Furthermore, when children unconsciously use this Bayesian statistical analysis, they may actually be better than adults at considering unusual possibilities. In a study published in 2014 in *Cognition,* my colleagues and I showed four-year-olds and adults a blicket detector that worked in an odd way, requiring two blocks on it together to make it go. The four-year-olds were better than the adults at grasping this unusual causal structure. The adults seemed to rely more on their prior knowledge that things usually do not work that way, even though the evidence implied otherwise for the machine in front of them.

In other recent research my group found that young children who think they are being instructed modify their statistical analysis and may become less creative as a result. The experimenter showed four-year-olds a toy that would play music if you performed the right sequence of actions on it, such as pulling a handle and then squeezing a bulb. For some children, the experimenter said, "I don't know how this toy works—let's figure it out." She proceeded to try out various longer-action sequences for the children, some that ended with the short sequence and made music and some that did not. When she asked the children to make the toy work, many of them tried the correct short sequence, astutely omitting actions that were probably superfluous based on the statistics of what they had seen.

With other children, the experimenter said that she would teach them how the toy worked by showing them sequences that did and did not produce music, and then she acted on the toy in exactly the same way. When asked to make the toy work, these children never tried a shortcut. Instead they mimicked the entire sequence of actions. Were these children ignoring the statistics of what they saw? Perhaps not—their behavior is accurately described by a Bayesian model in which the "teacher" is expected to choose the most instructive sequences. In simple terms: if she knew shorter sequences worked, she would not have shown them the unnecessary actions.

EVOLUTION AND NEUROLOGY

IF THE BRAIN is a computer designed by evolution, we can also ask about the evolutionary justification and neurological basis for the extraordinary learning abilities we see in very young children. Recent biological thinking is in close accord with what we see in the psychology lab.

From an evolutionary perspective, one of the most striking things about human beings is our long period of immaturity. We have a much longer childhood than any other species. Why make babies so helpless for so long and thus require adults to put so much work and care into keeping their babies alive?

Across the animal kingdom, the intelligence and flexibility of adults are correlated with the immaturity of babies. "Precocial" species such as chickens rely on highly specific innate capacities adapted to one particular environmental niche, and so they mature quickly. "Altricial" species (those whose offspring need care and feeding by parents) rely on learning instead. Crows, for instance, can take a new object, such as a piece of wire, and work out how to turn it into a tool, but young crows depend on their parents for much longer than chickens.

A learning strategy has many advantages, but until learning takes place, you are helpless. Evolution solves this problem with a division of labor between babies and adults. Babies get a protected time to learn about their environment, without having to actually do anything. When they grow up, they can use what they have learned to be better at surviving and reproducing—and taking care of the next generation. Fundamentally, babies are designed to learn.

Neuroscientists have started to understand some of the brain mechanisms that allow all this learning to occur. Baby brains are more flexible than adult brains. They have far more connections between neurons, none of them particularly efficient, but over time they prune out unused connections and strengthen useful ones. Baby brains also have a high level of the chemicals that make brains change connections easily.

The brain region called the prefrontal cortex is distinctive to humans and takes an especially long time to mature. The adult capacities for focus, planning and efficient action that are governed by this brain area depend on the long learning that occurs in childhood. This area's wiring may not be complete until the mid-20s.

The lack of prefrontal control in young children naturally seems like a huge handicap, but it may actually be tremendously helpful for learning. The prefrontal area inhibits irrelevant thoughts or actions. But being uninhibited may help babies and young children to explore freely. There is a trade-off between the ability to explore creatively and learn flexibly, like a child, and the ability to plan and act effectively, like an adult. The very qualities needed to act efficiently—such as swift automatic processing and a highly pruned brain network—may be intrinsically antithetical to the qualities that are useful for learning, such as flexibility.

A new picture of childhood and human nature emerges from the research of the past decade. Far from being mere unfinished adults, babies and young children are exquisitely designed by evolution to change and create, to learn and explore. Those capacities, so intrinsic to what it means to be human, appear in their purest forms in the earliest years of our lives. Our most valuable human accomplishments are possible because we were once helpless dependent children and not in spite of it. Childhood, and caregiving, is fundamental to our humanity. SA

Alison Gopnik is professor of psychology and affiliate professor of philosophy at the University of California, Berkeley. She has done groundbreaking research into how children develop a "theory of mind," the ability to understand that other people have minds and may believe or want different things than they do. She helped to formulate the "theory theory," the idea that children learn in the same way that scientists do. Investigations of children's minds, she argues, could help us resolve deep philosophical questions such as the mystery of consciousness.

MORE TO EXPLORE

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SLEEP ON IT!

Your nightly rest turns out to affect your mind and health more than anyone suspected

By Robert Stickgold

"Do I really need to sleep?"

As I travel around the world talking about sleep, I am asked this question over and over. The answer has always been clear—yes, everyone needs to do it. Just like hunger, thirst and sexual desire, the urge to sleep is a physiological drive. Exactly what spending a third of our lives unconscious gets us, however, has long mystified scientists.

Illustration by Maria Corte Maidagan

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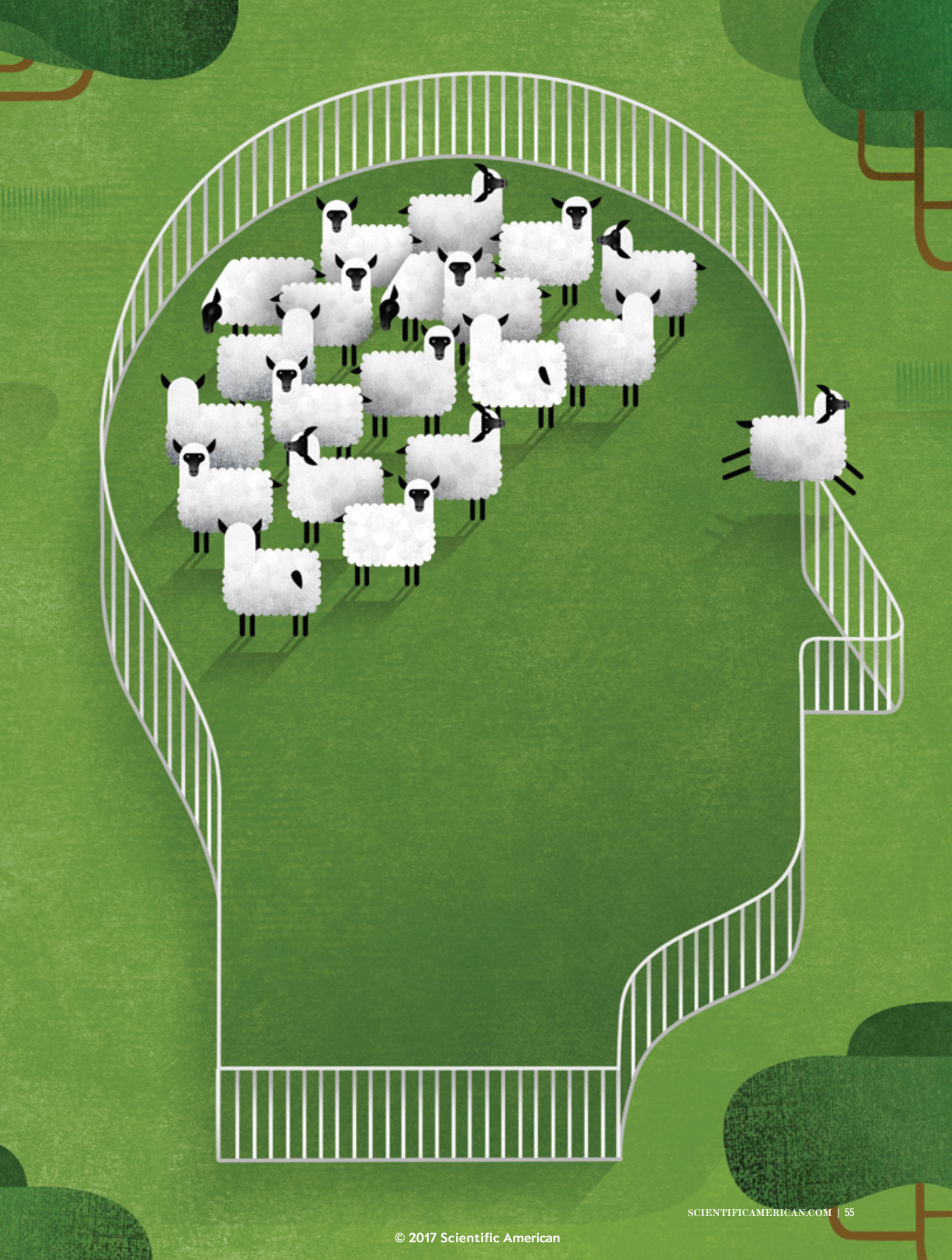

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In acknowledging our lack of an answer, Allan Rechtschaffen, one of the world's foremost sleep researchers, said in 1978, "If sleep does not serve an absolutely vital function, then it is the *biggest mistake* the evolutionary process has ever made" (emphasis mine). In the 1990s J. Allan Hobson, another leading sleep researcher, quipped that the only known function of sleep was to cure sleepiness.

Research over the past 20 years has finally begun to provide at least a partial explanation for why we must sleep. The clearest finding is that sleep does not serve just a single purpose. Instead it appears to be needed for the optimal functioning of a multitude of biological processes—from the inner workings of the immune system to proper hormonal balance, to emotional and psychiatric health, to learning and memory, to the clearance of toxins from the brain. At the same time, none of these functions fails completely in the absence of sleep. In general, sleep seems to *enhance* the performance of these systems instead of being absolutely necessary. And yet anyone who lives for months without sleep will die.

Even this imperfect understanding has taken decades to develop. By the end of the 20th century researchers had replaced ancient notions about sleep—that it was caused by blood retreating from the surface of the skin or by the buildup of warm vapors from the stomach—with detailed measurements of brain-wave activity, breathing patterns, and daily oscillations in the amount of hormones and other molecules in the blood. More recently, investigators have begun identifying the exact aspects of sleep that are important for each of its benefits. Ironically, though, the more researchers uncover about the unconditional necessity of a good night's sleep for the proper functioning of mind and body, the less time 21st-century citizens spend in the soothing arms of Morpheus, the Greek god of dreams.

FATAL INSOMNIA

THE CLEAREST EVIDENCE of our absolute need for sleep comes from a study published in 1989 by Carol Everson based on work she did while at Rechtschaffen's laboratory. Everson, now at the Medical College of Wisconsin, found that rats totally deprived of sleep all died within a month. In actuality, all she had to do to achieve this fatal result was to prevent the animals from entering the stage of sleep characterized by rapid eye movement (REM). But a quarter of a century later researchers still cannot explain *why* the rats died. A series of experiments in the intervening years has only served to eliminate possible causes; it is not caused by, for example, increased stress, excessive energy consumption, or failure of the body's internal heat regulators or the immune system.

Death by sleep deprivation is not unique to rats. Fatal familial insomnia, first described about 30 years ago, is, as the name suggests, a heritable human disorder that leads first to unremitting insomnia and thence to death. A team of Italian researchers, then at the University of Bologna's medical school, reported it in 1986. The group, led by the late Elio Lugaresi and Rossella Medori, told the story of a 53-year-old man who died within months of developing intractable insomnia—as had many of his relatives over two generations. Postmortem analysis of his brain showed massive loss of nerve cells in two regions of the thalamus, a structure about the size of a walnut that is found in the midbrain and generally acts as a way station for incoming sensory input. The two particular regions in question, however, are known more for their role in regulating emotional memory and producing so-called sleep spindles, a key pattern of waves found in electroencephalograms of the sleeping brain.

How this deterioration in the thalamus might lead either to insomnia or to death is unclear. But the immediate cause of the damage itself is now known. In the early 1990s Medori, by then at Case Western Reserve University, and her colleagues determined that a malformed protein, called a prion, was responsible for the destruction. Prions are also known to cause scrapie in sheep and bovine spongiform encephalopathy ("mad cow disease") in humans—though in the case of fatal familial insomnia, the prion is inherited from one generation to the next rather than being ingested from the environment, as in the other two ailments.

Fortunately, there are no other reported instances of human death caused by sleep deprivation (aside from accidental deaths when, for example, a sleepless driver falls asleep at the wheel). But there are also no other reports of people going several months without sleep. We are thus left with two examples of prolonged and total sleep deprivation leading to death—experimentally induced sleep deprivation in rats and a heritable prion disease in humans—and with no understanding of the exact cause of death in either case.

ANTIBODIES AND HORMONES

MEANWHILE WE DO KNOW that as little as one night of complete or even partial sleep loss can interfere with various bodily functions, such as hormonal activity and protection against infections. Two studies looking at the body's response to immunization with hepatitis vaccines show how dramatic the effects of sleep deprivation can be on the immune system. In the first experiment, from 2003, a small group of college students received a standard hepatitis A vaccination consisting of inactivated virus in the morning, after which investigators permitted half of them to sleep normally; the other half were kept awake all night.

The sleep-deprived subjects were not allowed any sleep until the following night. Four weeks later researchers took blood samples from the students and measured the amount of protective antibodies that their immune system had produced in response to the virus in the vaccine. Higher levels of antibodies would indicate a better response to the vaccine and thus likely greater protection against future infection with disease-causing versions of the virus. After the four weeks, the group that had enjoyed a normal night's sleep had 97 percent higher

IN BRIEF

Many studies—not to mention common experience—support the link between a good night's sleep and improved mood, memory and learning.

A growing number of experiments carried out over the past two decades have also found that the mechanism of sleep directly affects other workings of the body, from hormonal balance to immune protection.

Despite these findings, researchers still do not understand exactly why we need our daily visit to the land of Nod, but they are learning a great deal about what precisely happens physiologically when we sleep.

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antibody levels than the one that had been sleep-deprived.

Negative effects are measurable with less than a full night's sleep as well. In the second study, adults received the standard three doses of hepatitis B vaccine over the course of six months. (Repeat vaccination is required to build up full immune protection.) Researchers gave each participant a motion detector similar to a watch, which monitored their sleep at home. By comparing the subjects' average amount of sleep during the week of their first shot to the level of antibody protection they displayed after the second shot, investigators determined that antibody levels increased 56 percent for every additional hour of sleep. Six months after the final vaccination, those who had averaged less than six hours of sleep a night during the week around the first vaccination were seven times more likely to have such low amounts of antibodies in their blood that they were considered unprotected against future infection with the hepatitis B virus. Even otherwise healthy children with sleep disturbances show immune deficits. This year Zihe Zhang of Shandong University in China and colleagues examined the immune status of 50 children with obstructive sleep apnea. Based on changes in the concentrations of T lymphocytes and other immune-related indices in their blood, the researchers concluded that sleep apneas led to impaired immune function in these children.

Impressive evidence for impaired hormonal function came from a series of studies performed by Karine Spiegel, who was at that time working with Eve Van Cauter of the University of Chicago. In one of these experiments, researchers allowed 11 healthy young men to get just four hours of sleep a night. After five nights of restricted sleep, the men's ability to clear glucose from the blood—a process that the hormone insulin manages—was reduced by 40 percent. In a separate study, Spiegel and her colleagues similarly limited the amount of sleep of 12 men for two nights. The scientists measured the amount of ghrelin, an appetite-stimulating hormone, found in the volunteers' blood and found it had jumped by 28 percent. At the same time, amounts of a different hormone, known as leptin, decreased by 18 percent; leptin inhibits hunger by signaling the brain that there is no need to eat. Not surprisingly, the sleep-deprived men reported an average 23 percent increase in their hunger levels.

Taken as a whole, these studies of human physiology suggest that reduced sleep could lead to increased weight gain—a hypothesis that is now supported by at least 50 other studies. In several investigations, children from six to nine years of age who got fewer than 10 hours of sleep were one and a half to two and a half times more likely to be obese, and studies in adults suggest a 50 percent increase in obesity among participants with fewer than six hours of sleep. Research also shows an association between sleep restriction and the development of type 2 diabetes.

NEGATIVITY BOMB

DESPITE THE REMARKABLE EFFECTS of restricted sleep on immune and hormonal function, its greatest impact probably occurs in the brain. In a 2006 study I conducted with Matthew P. Walker, now at the University of California, Berkeley, we looked at how a single night of sleep deprivation affected the emotional memories that people laid down. Twenty-six subjects—half of whom had been sleep-deprived the night before—were shown positive, negative and neutral words (for example, "calm," "grief" or "willow") and asked to rate their emotionality. Then, after two nights of recovery sleep, they were given a surprise memory test.

Compared with the subjects who had slept normally, those

FINDINGS

Don't Skimp on Sleep

Research has uncovered many ways that sleep deprivation impairs mental and physical health. Some of the best-studied and most significant impacts are highlighted here.

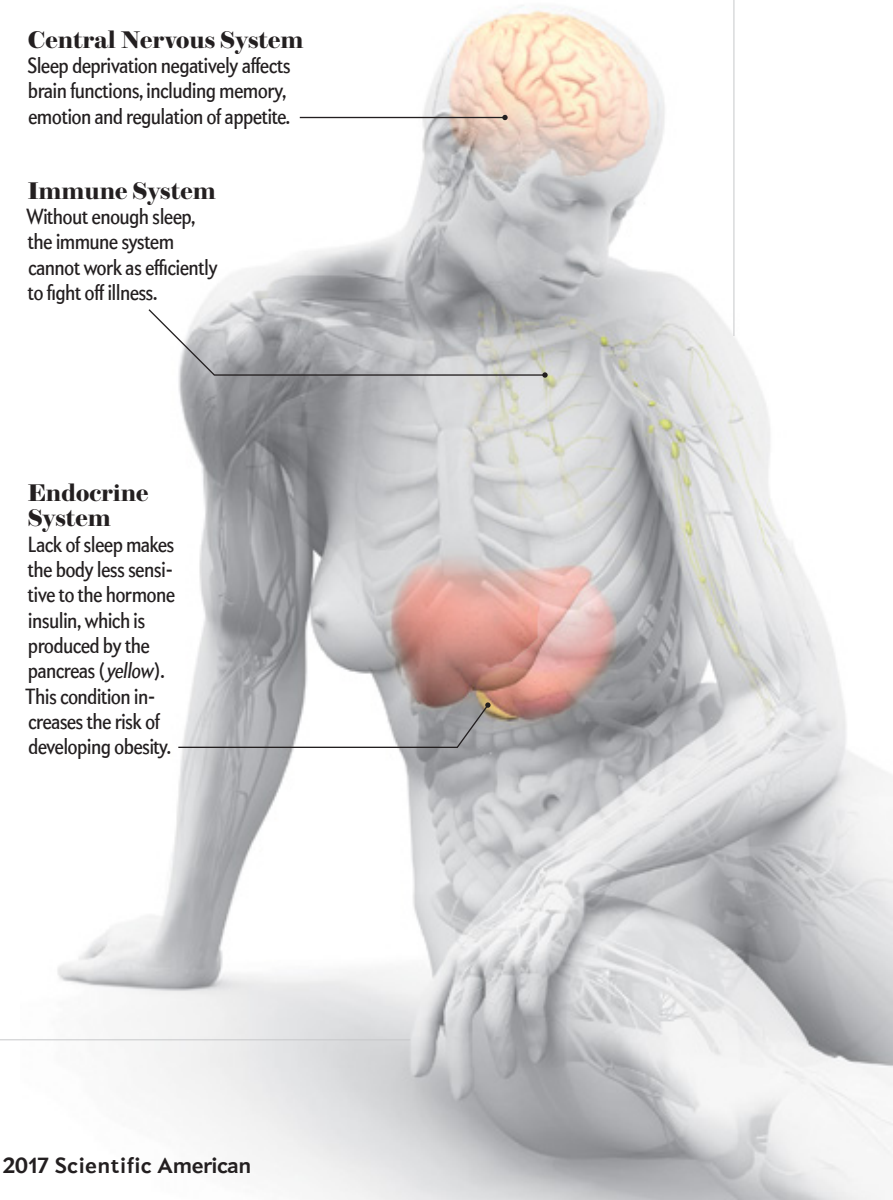
Central Nervous System
Sleep deprivation negatively affects brain functions, including memory, emotion and regulation of appetite.
Immune System
Without enough sleep, the immune system cannot work as efficiently to fight off illness.
Endocrine System
Lack of sleep makes the body less sensitive to the hormone insulin, which is produced by the pancreas (yellow). This condition increases the risk of developing obesity.

Illustration by Bryan Christie

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who were sleep-deprived before seeing the words for the first time showed a 40 percent deterioration in their ability to recognize them. But more striking was the relative impact of sleep deprivation on the three categories of words. When subjects were sleep-deprived, their recognition of positive and neutral words both deteriorated by 50 percent. Their ability to recognize words with negative connotations, however, deteriorated only 20 percent. In contrast, the memory formed after normal sleep for positive and negative words differed little, with neutral words being less memorable than either positive or negative words. In other words, the memory of negative words appeared to be at least twice as strong as positive or neutral words after study volunteers were forced to cut back on their sleep.

WHEN YOU ARE SLEEP-DEPRIVED, YOU FORM TWICE AS MANY MEMORIES OF NEGATIVE EVENTS IN YOUR LIFE AS OF POSITIVE EVENTS.

This result suggests the rather horrifying possibility that when you are sleep-deprived, you effectively form twice as many memories of negative events in your life as of positive events, producing a biased—and potentially depressing—memory of your day. Indeed, several studies over the past 25 years have now concluded that poor sleep can, under certain circumstances, lead to depression severe enough to be diagnosed as major depression and may contribute to other psychiatric disorders as well.

The evidence of a causal link with depression in particular has grown in recent years and comes to a large extent from studies of sleep apnea, a disorder in which the flow of air into the lungs becomes interrupted during sleep. It may lead to snoring, gasping and other disruptions of respiration. Each time individuals with sleep apnea briefly stop breathing, they awaken momentarily to start breathing again. As a result, sufferers of severe apnea might wake up every minute or two throughout the night. A 2012 study by the U.S. Centers for Disease Control and Prevention found that men and women with a diagnosis of sleep apnea are, respectively, 2.4 and 5.2 times more likely to have major depression compared with their better-rested counterparts.

Of course, finding a correlation between these two conditions is not the same thing as proving that one causes the other. But a recent analysis of 19 studies found that treating sleep apnea with so-called CPAP devices (for *c*ontinuous *p*ositive *a*irway *p*ressure), which restore normal breathing and sleep, significantly reduces symptoms of depression. Indeed, one of the studies, which coincidentally had included a greater percentage of depressed patients at the outset than the others, found a 26 percent reduction in depression symptoms in CPAP users.

These results still do not prove conclusively that fitful sleep can bring on depression, nor was the effect of the CPAP treatment compared with that of antidepressant medication. Nevertheless, these suggestive findings deserve further investigation. Similarly, a 2007 study found that treatment of apnea in children who also had attention-deficit/hyperactivity disorder led to a 36 percent decrease in hyperactivity symptom ratings—a significantly larger reduction than the 24 percent achieved with typical ADHD medications.

FUTURE MEMORIES

ALTHOUGH RESEARCHERS still do not know the physiological mechanism by which sleep and its lack affect mental health, they suspect that the role sleep plays in helping the brain transform people's daily experiences into memories has a lot to do with it. The past two decades have seen an explosion of discoveries showing that sleep participates in memory processing in everyone—no matter what their emotional state. Among the findings: sleep after learning leads to the selective stabilization, strengthening, integration and analysis of new memories. In doing so, it controls what we remember and how we remember it.

In the late 19th and early 20th century scientists considered memories to be fragile until they went through a process of so-called consolidation, which transformed them into a stable form that could last a lifetime. More recent research has shown that memories retain the ability to change even after the brain records and consolidates them. Indeed, reactivation of a memory can return it to an unstable state long after it was first formed, requiring reconsolidation; while in this labile form, it can be changed or lost altogether. This finding is both a curse and a blessing—a curse because originally accurate information can be corrupted and a blessing because inaccurate information can be corrected. Researchers have thus begun to talk about memory *evolution* instead of memory consolidation, especially when discussing sleep-dependent memory processing.

The modern era of research into sleep and memory began just over 20 years ago, when Avi Karni and his colleagues in Israel demonstrated that subjects trained on a visual-discrimination task actually improved over a night of sleep but only if they were allowed to enter REM sleep. (As an aside, most dreams take place during REM sleep.) Their experiment showed that sleep does more than just stabilize memories, keeping them from deteriorating over time; it actually improves them.

In 2000 Walker came into my office waving a journal article and predicting, "This one is sleep-dependent, too!" The paper described a task in which subjects learned to tap out a particular sequence of finger movements, which became easier for them to do over time, even without additional practice. Still, the authors had not looked at how sleep might contribute to this improvement. Within two weeks Walker had the answer. He found that sleep had indeed improved their performance, and he later determined that the benefit depended on experiencing a light stage of non-REM sleep rather than of REM sleep, as in the Karni vision experiments. The inescapable conclusion: the brain strengthens different types of memories during different stages of sleep.

Further research showed that not all memories undergo this sleep-dependent stabilization. In 2008 Jessica Payne, now at the University of Notre Dame, conducted a study in which she showed volunteers various scenes with aversive objects—such as a dead cat in the middle of a road. She found that after a night of sleep the subjects could accurately recognize the image of the dead cat, but they had forgotten the background street scene.

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What was most impressive was that this selective forgetting of the background details did not happen when she trained subjects in the morning and then tested them in the evening after a day spent awake. And it did not happen if the central image was nonaversive—for example, if it was just a cat crossing the road. Thus, sleep, but not wakefulness, caused the brains of the study participants to retain the highly emotional central images in preference to either the neutral images (cat crossing the road) or their background scenes.

But it is not just emotional memories that are preferentially enhanced during sleep. It appears that anything you think is important will be selectively retained while you are asleep. Two groups in Europe have shown that telling subjects who have been trained on a particular task that they will or will not be tested on that information after they sleep affects what happens during that sleep. As you might expect, only the information that subjects are told they will be retested on shows improvement the next day. In contrast, when subjects are trained in the morning, informing them that they will or will not be tested that evening does not seem to make any difference. Sleep, then, and not wakefulness, selectively strengthens memories that the brain deems valuable.

These findings support the arguments of Daniel Schacter of Harvard University that memory is about the future, not about the past. He has argued that we have evolved memory systems not so we can reminisce about the past but so we can use prior experience to enhance our future performance. In this context, it is not surprising that sleep seems to care most about information that is likely to be of future relevance. When we talk about sleeping on a problem, we are not merely asking the sleeping brain to remember something. We want our brain to take the information that is already stored there and do some kind of calculation, to juxtapose different possibilities, to find the best solution to a problem. Lucky for us, it can!

An example of this analytic ability is highlighted in a weather-prediction experiment developed by Barbara J. Knowlton and her colleagues at the University of California, Los Angeles. Knowlton showed subjects one or more cards from a set of four—each of which displayed a particular geometric design (circles, diamonds, squares or triangles). Before the subjects began the task, the researchers assigned each card to a particular imaginary weather outcome—rainy or sunny—without sharing the information with the participants. Then, based on the cards shown, investigators asked those participants to predict whether the cards indicated the weather would be rainy or sunny. Over time subjects got a sense of how the cards related to the weather. For example, the first trial might show the diamonds card, and the weather, the subjects are told, turns out to be sunny. Then, on the second trial, the circles and triangles cards are both displayed, and the weather turns out to be rainy. Even after just these two trials, subjects inevitably would begin to construct hypotheses about the relations, such as that diamonds mean sunshine. But then, on the third trial, the diamonds card might appear again, only to be followed by rain.

The trick here is that the cards are only *probabilistically* related to the weather. Thus, the diamonds card predicts sun 80 percent of the time, but for the other 20 percent, it is followed by rain. Other cards end up predicting sun just 20 to 60 percent of the time. In Knowlton's study, even after 200 trials, subjects still had not mastered the task, guessing the most likely outcome only about 75 percent of the time.

Use of such tasks has allowed researchers to discriminate between different memory systems within the brain—those involved in remembering facts (the "what" system) and those involved in learning skills (the "how" system). As subjects train on the weather-prediction task, they slowly shift from using the *what* system to the *how* system. When Ina Djonlagic in my lab asked what happens to this information with sleep, she obtained an amazing result. When volunteers who had trained in the morning were retested the same evening, they also performed at around 75 percent, apparently fully retaining the information they had learned that morning. But when other subjects were trained in the evening and tested after a night of sleep, they were 10 percent better at predicting the outcome than they had been the evening before. Somehow the sleeping brain was actually able to improve participants' understanding of the relation between the cards and the subsequent weather. They had gained a better model of how the world worked.

The more researchers explore what happens while we sleep, the more they discover new benefits to a good night's sleep. The most recent possible addition to the list is the clearance of waste products from the brain. In 2013 Lulu Xie and her colleagues at the University of Rochester Medical Center reported that the space between cells in the brain increases during sleep, allowing for better flow of cerebrospinal fluid between the brain and the spine. When the investigators injected beta-amyloid (the precursor of the amyloid plaques found between neurons in Alzheimer's disease) into mice, they found that it was cleared from the brain during sleep at twice the rate seen in awake animals. Presumably the increased flow of cerebrospinal fluid helped to move the potentially toxic molecule out of the brain, away from the areas where it could cause the most damage. Now researchers would like to find out whether the increased flow normally seen during sleep is impaired in people who have Alzheimer's.

Given all the latest research on the many functions of sleep and the likelihood that yet more will be discovered, skimping on sleep is looking like a worse and worse strategy for dealing with the demands of daily life. Taken together, the results of studies looking at the role of sleep in hormonal, immunological and memory functions suggest that if you do not get enough, you could—besides being very tired—wind up sick, overweight, forgetful and very blue. SA

Robert Stickgold is director of the Center for Sleep and Cognition at Beth Israel Deaconess Medical Center and an associate professor at Harvard Medical School.

MORE TO EXPLORE

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mind of the meditator

Contemplative practices that extend back thousands of years show a multitude of benefits for both body and mind

By Matthieu Ricard, Antoine Lutz and Richard J. Davidson

Illustration by Marcos Chin

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WHEN THE SOCIETY FOR NEUROSCIENCE ASKED TENZIN GYATSO, the 14th Dalai Lama (the leader of Tibetan Buddhism), to address its annual meeting in Washington, D.C., in 2005, a few hundred members among the nearly 35,000 or so attending the meeting petitioned to have the invitation rescinded. A religious leader, they felt, had no place at a scientific meeting. But this particular leader turned out to have a provocative and ultimately productive question to pose to the gathering. "What relation," he asked, "could there be between Buddhism, an ancient Indian philosophical and spiritual tradition, and modern science?"

The Dalai Lama, putting action before rhetoric, had already started trying to find answers to his own question. Back in the 1980s, he had sparked a dialogue about science and Buddhism, which led to the creation of the Mind & Life Institute, dedicated to studying contemplative science. In 2000 he brought new focus to this endeavor: he launched the subdiscipline of "contemplative neuroscience" by inviting scientists to study the brain activity of expert Buddhist meditators—defined as having more than 10,000 hours of practice.

For nearly 15 years more than 100 monastics and lay practitioners of Buddhism and a large number of beginning meditators have participated in scientific experiments at the University of Wisconsin–Madison and at least 19 other universities. The article you are reading, in fact, is the product of a collaboration between two neuroscientists and a Buddhist monk who originally trained as a cell biologist.

A comparison of the brain scans of meditators with tens of thousands of hours of practice with those of neophytes and nonmeditators has started to explain why this set of techniques for training the mind holds great potential for supplying cognitive and emotional benefits. The goals of meditation, in fact, overlap with many of the objectives of clinical psychology, psychiatry, preventive medicine and education. As suggested by the growing compendium of research, meditation may be effective in treating depression and chronic pain and in cultivating a sense of overall well-being.

The discovery of meditation's benefits coincides with recent neuroscientific findings showing that the adult brain can still be deeply transformed through experience. These studies show that when we learn how to juggle or play a musical instrument, the brain undergoes changes through a process called neuroplasticity. A brain region that controls the movement of a violinist's fingers becomes progressively larger with mastery of the instrument. A similar process appears to happen when we meditate. Nothing changes in the surrounding environment, but the meditator regulates mental states to achieve a form of inner enrichment, an experience that affects brain functioning and its physical structure. The evidence amassed from this research has begun to show that meditation can rewire brain circuits to produce salutary effects not just on the mind and the brain but on the entire body.

IN BRIEF

Meditation is an ancient pursuit that, in some form, is a part of nearly every world religion. In recent years its practice, derived from various branches of Buddhism, has made its way into the secular world as a means of promoting calmness and general well-being.

Three common forms of meditation—focused attention, mindfulness and compassion—are now practiced everywhere, from hospitals to schools, and have increasingly become an object of scrutiny in scientific laboratories worldwide.

Physiological changes in the brain—an altered volume of tissue in some areas—occur through meditation. Practitioners also experience beneficial psychological effects: they react faster to stimuli and are less prone to various forms of stress.

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Contemplative Experiences

Advances in neuroimaging and other technologies have enabled scientists to gain insight into what happens in the brain during three major forms of Buddhist meditation—focused attention, mindfulness, and compassion and loving kindness. The diagram offers a glimpse into the cycle of events that occurs in the practice of focused-attention meditation—and the corresponding activation of specific brain areas.

Focused Attention

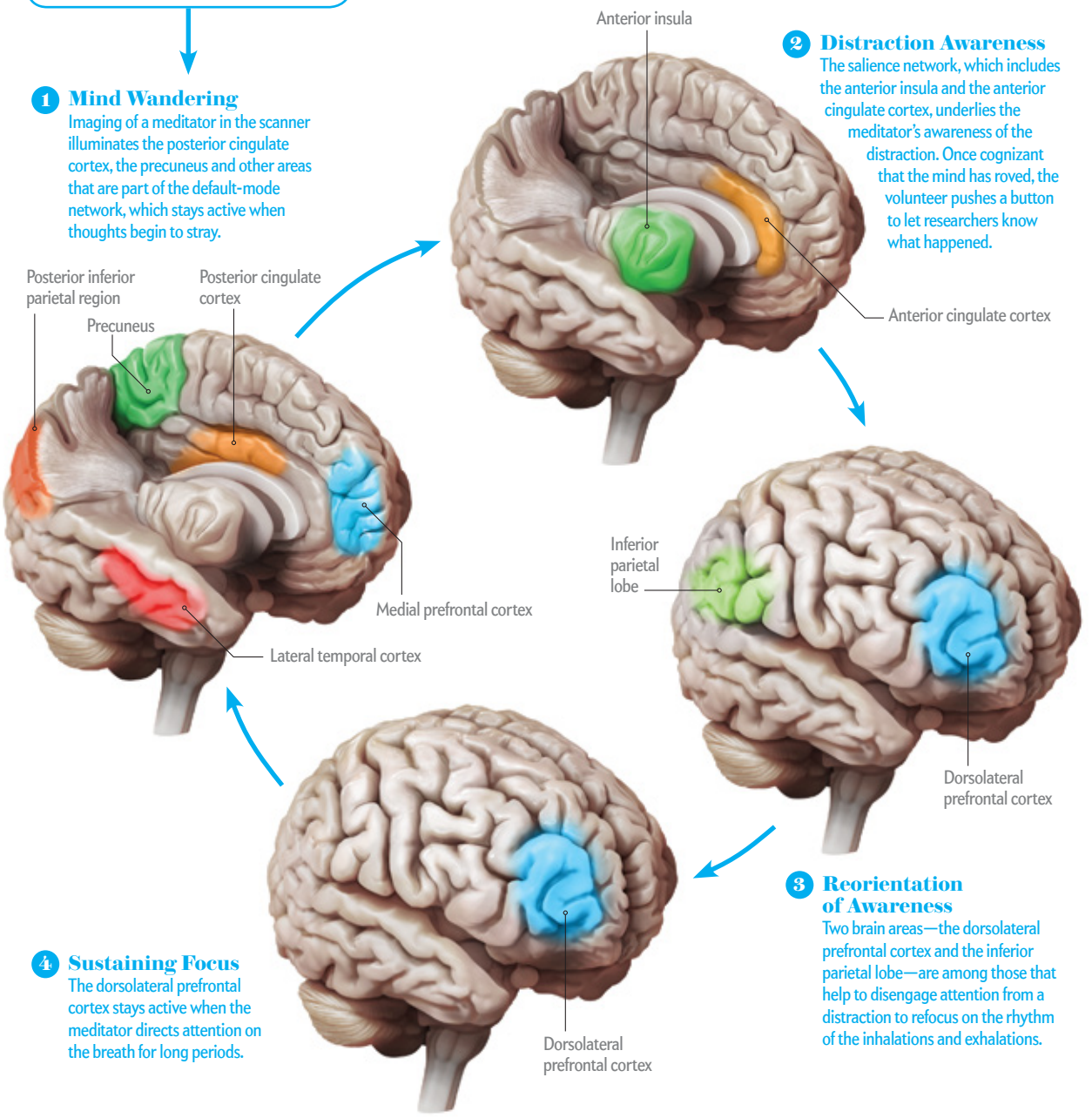
This practice typically directs the meditator to concentrate on the in-and-out cycle of breathing. Even for the expert, the mind wanders, and the object of focus must be restored. A brain-scanning study at Emory University has pinpointed distinct brain areas that become involved as attention shifts.

Mindfulness

Also called open-monitoring meditation, mindfulness entails observing sights, sounds and other sensations, including internal bodily sensations and thoughts, without being carried away by them. Expert meditators have diminished activity in anxiety-related areas, such as the insular cortex and the amygdala.

Compassion and Loving Kindness

In this practice, the meditator cultivates a feeling of benevolence directed toward other people, whether friend or enemy. Brain regions that fire up when putting oneself in the place of another—the temporoparietal junction, for instance—show an increase in activity.



1 Mind Wandering
Imaging of a meditator in the scanner illuminates the posterior cingulate cortex, the precuneus and other areas that are part of the default-mode network, which stays active when thoughts begin to stray.

2 Distraction Awareness
The salience network, which includes the anterior insula and the anterior cingulate cortex, underlies the meditator's awareness of the distraction. Once cognizant that the mind has roved, the volunteer pushes a button to let researchers know what happened.

3 Reorientation of Awareness
Two brain areas—the dorsolateral prefrontal cortex and the inferior parietal lobe—are among those that help to disengage attention from a distraction to refocus on the rhythm of the inhalations and exhalations.

4 Sustaining Focus
The dorsolateral prefrontal cortex stays active when the meditator directs attention on the breath for long periods.

Illustration by David C. Killpack

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WHAT IS MEDITATION?

MEDITATION HAS ROOTS in the contemplative practices of nearly every major religion. The prevalence of meditation in the media has given the word various meanings. We will refer to meditation as the cultivation of basic human qualities, such as a more stable and clear mind, emotional balance, a sense of caring, even love and compassion—qualities that remain latent as long as one does not make an effort to develop them. It is also a process of familiarization with a more serene and flexible way of being.

In principle, meditation is relatively simple and can be done anywhere. No equipment or workout attire is needed. The meditator begins by assuming a comfortable physical posture, neither too tense nor too lax, and by wishing for self-transformation and a desire for others' well-being and for the alleviation of their suffering. Later the practitioner must stabilize the mind, which is too often disorderly—and occupied by a stream of inner chatter. Mastering the mind requires freeing it from automatic mental conditioning and inner confusion.

We will examine here what happens in the brain during three common types of meditation developed through Buddhism and now practiced in secular programs in hospitals and schools throughout the world. The first one, focused-attention meditation, aims to tame and center the mind in the present moment while developing the capacity to remain vigilant to distractions. The second one, mindfulness, or open-monitoring meditation, tries to cultivate a less emotionally reactive awareness to emotions, thoughts and sensations occurring in the present moment to prevent them from spiraling out of control and creating mental distress. In mindfulness, the meditator remains attentive, moment by moment, to any experience without focusing on anything specific. Finally, another type of practice is known in Buddhist tradition as compassion and loving kindness and fosters an altruistic perspective toward others.

UNDER THE SCANNER

NEUROSCIENTISTS HAVE NOW BEGUN to probe what happens inside the brain during the various types of meditation. Wendy Hasenkamp, then at Emory University, and her colleagues used brain imaging to identify the neural networks activated by focused-attention meditation. In the scanner, the participants trained their attention on the sensation produced by breathing. Typically during this form of meditation, the mind wanders from an object, and the meditator must recognize this and then restore attention to the gradual rhythm of the inhaling and exhaling. In this study, the meditator had to signal mind wandering by pressing a button. Researchers identified four phases of a cognitive cycle: an episode of mind wandering, a moment of becoming aware of the distraction, a phase of reorienting attention and a resumption of focused attention.

Each of the four phases involves particular brain networks. The first part of the cycle, when a distraction occurs, increases activity in the wide-ranging default-mode network (DMN). This network includes areas of the medial prefrontal cortex, the posterior cingulate cortex, the precuneus, the inferior parietal lobe and the lateral temporal cortex. The DMN is known to become activated during mind wandering and to play a general role in building and updating internal models of the world based on long-term memories about the self or others.

The second phase, becoming aware of a distraction, occurs in other brain areas such as the anterior insula and the anterior cingulate cortex, regions of what is called the salience network. This network regulates subjectively perceived feelings, which might, for instance, lead to being distracted during a task. The salience network is thought to play a key role in detecting novel events and in switching activity during meditation among assemblies of neurons that make up the brain's large-scale networks. It may shift attention away from the default-mode network, for instance.

The third phase engages additional areas—among them the dorsolateral prefrontal cortex and the lateral inferior parietal lobe—that "take back" one's attention by detaching it from any distracting stimulus. Finally, in the fourth and last phase, the dorsolateral prefrontal cortex continues to retain a high level of activity, as the meditator's attention remains directed toward an object such as the breath.

In our laboratory at Wisconsin, we further observed different patterns of activity depending on a practitioner's level of experience. Veteran meditators with more than 10,000 hours of practice showed more activity in these attention-related brain regions compared with novices. Paradoxically, the most experienced meditators demonstrated less activation than the ones without as much experience. Advanced meditators appear to acquire a level of skill that enables them to achieve a focused state of mind with less effort. These effects resemble the skill of expert musicians and athletes capable of immersing themselves in the "flow" of their performances with a minimal sense of effortful control.

To study the impact of focused-attention meditation, we also studied its volunteers before and after a three-month retreat with intensive meditation exercises for at least eight hours a day. They received headphones that broadcast sounds at a given frequency, occasionally mixed with slightly higher-pitched sounds. They had to focus on the sounds played in one ear for 10 minutes and react to periodically interspersed high-pitched tones. After the retreat, we found that meditators, compared with a nonmeditating control group, showed less trial-to-trial variation in their reaction times on this highly repetitive task, which lent itself easily to distractions. The result suggested that the meditators had an enhanced capacity to remain vigilant. The brain's electrical responses to high-pitched tones remained more stable at the second session only for the meditators.

STREAM OF CONSCIOUSNESS

THE SECOND TYPE of well-studied meditation also involves another form of attention. Mindfulness, or open-monitoring meditation, requires the meditator to take note of every sight or sound and track internal bodily sensations and inner self-talk. The person stays aware of what is happening without becoming overly preoccupied with any single perception or thought, returning to this detached focus each time the mind strays. As awareness of what is happening in one's surroundings grows, normal daily irritants—an angry colleague at work, a worried child at home—become less disruptive, and a sense of psychological well-being develops.

With Heleen Slagter, then in our group at Wisconsin, we sought to learn about the influence of this form of training on mental functioning by measuring the participants' capacity to detect rapidly presented visual stimuli—a means to measure

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INNER PATHWAYS of brain activity register on an electroencephalogram as co-author Matthieu Ricard meditates.

JEFF MILLER University of Wisconsin–Madison

mindfulness meditation, which is also sometimes called nonreactive awareness. To perform this experiment, we used a task in which the participants had to detect two numbers presented on a screen rapidly, amid a succession of letters. If the second number appears about 300 milliseconds after the first one, subjects often do not see the second, a phenomenon known as attentional blink.

If the second number appears after a delay of 600 milliseconds, it can be detected without difficulty. The attentional blink reflects the limits of the brain's ability to process two stimuli presented to the observer at close intervals. When too much of the brain's attention is devoted to processing the first number, the second number cannot always be detected, although the observer usually can see it on some of the trials. We hypothesized that mindfulness training could reduce the propensity to "get stuck," or absorbed by seeing the first number. Mindfulness practice cultivates a nonreactive form of sensory awareness, which should result in a reduced attentional blink. As we predicted, after three months of an intensive retreat, the meditators perceived both numbers more frequently than the controls did. This improved perception was also reflected in lessened activity of a particular brain wave in response to the first number. Monitoring the P3b brain wave, used to assess how attention is allocated, indicated that meditators were capable of optimizing attention so as to minimize the attentional blink.

Staying aware of an unpleasant sensation can reduce maladaptive emotional responses and help one to move beyond the disagreeable feeling and may be particularly useful in dealing with pain. In our Wisconsin lab, we have studied experienced practitioners while they performed an advanced form of mindfulness meditation called open presence. In open presence, sometimes called pure awareness, the mind is calm and relaxed, not focused on anything in particular yet vividly clear, free from excitation or dullness. The meditator observes and is open to experience without making any attempt to interpret, change, reject or ignore painful sensation. We found that the intensity of the pain was not reduced in meditators, but it bothered them less than it did members of a control group.

Compared with novices, expert meditators' brain activity diminished in anxiety-related regions—the insular cortex and the amygdala—in the period preceding the painful stimulus. The meditators' brain response in pain-related regions became accustomed to the stimulus more quickly than that of novices after repeated exposures to it. Other tests in our lab have shown that meditation training increases one's ability to better control and buffer basic physiological responses—inflammation or levels of a stress hormone—to a socially stressful task such as giving a public speech or doing mental arithmetic in front of a harsh jury.

Several studies have documented the benefits of mindfulness on symptoms of anxiety and depression and its ability to improve sleep patterns. By deliberately monitoring and observing their thoughts and emotions when they feel sad or worried, depressed patients can use meditation to manage negative thoughts and feelings as they arise spontaneously and so lessen rumination. Clinical psychologists John Teasdale, then at the University of Cambridge, and Zindel Segal of the University of Toronto showed in 2000 that for patients who had previously suffered at least three episodes of depression, six months of mindfulness practice, along with cognitive therapy, reduced the risk of relapse by nearly 40 percent in the year following the onset of a severe depression. More recently, Segal demonstrated that the intervention is superior to a placebo and has a protective effect against relapse comparable to standard maintenance antidepressant therapy.

COMPASSION AND LOVING KINDNESS

THE THIRD FORM of meditation under study cultivates attitudes and feelings of loving kindness and compassion toward other people, whether they are close relatives, strangers or enemies. This practice entails being aware of someone else's needs and then experiencing a sincere, compassionate desire to help that person or to alleviate the suffering of other people by shielding them from their own destructive behavior.

To generate a compassionate state may sometimes entail the meditator feeling what another person is feeling. But having one's emotions resonate empathetically with the feelings of another person does not by itself suffice to yield a compassionate mindset. The meditation must also be driven by an unselfish desire to help someone who is suffering. This form of meditation

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on love and compassion has proved to be more than just a spiritual exercise. It has shown potential to benefit health care workers, teachers and others who run the risk of emotional burnout linked to the distress experienced from a deeply empathetic reaction to another person's plight.

The meditator begins by focusing on an unconditional feeling of benevolence and love for others, accompanied by silent repetition of a phrase conveying intent, such as "May all beings find happiness and the causes of happiness and be free from suffering and the causes of suffering." In 2008 we studied experienced volunteers who had practiced this form of training for thousands of hours and found an increase in activity in several brain regions while they listened to voices conveying distress. The secondary somatosensory and insular cortices, known to participate in empathetic and other emotional responses, were more activated for experts than controls in response to the distressed voice, suggesting an enhanced ability to share the feelings of others without reporting any sign of becoming emotionally overwhelmed. The practice of compassion meditation also produced more activity in areas such as the temporoparietal junction, the medial prefrontal cortex and the superior temporal sulcus, all typically activated when we put ourselves in the place of another.

More recently, Tania Singer of the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany, and Olga Klimecki of the University of Geneva, in collaboration with one of us (Ricard), sought to distinguish differences between the effects of empathy and compassion on meditators. They noted that compassion and altruistic love were associated with positive emotions, and they suggested that emotional exhaustion or burnout was, in fact, a kind of empathy "fatigue."

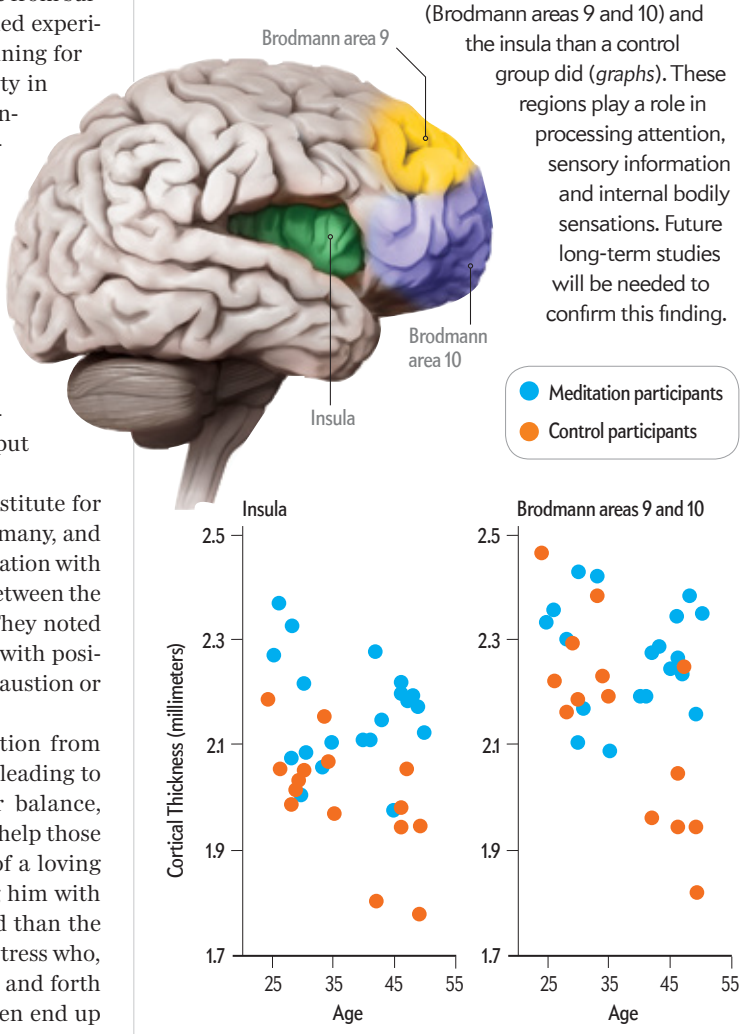
According to the Buddhist contemplative tradition from which this practice is derived, compassion, far from leading to distress and discouragement, reinforces an inner balance, strength of mind and a courageous determination to help those who suffer. If a child is hospitalized, the presence of a loving mother at his side holding his hand and comforting him with tender words will no doubt do that child more good than the anxiety of a mother overwhelmed with empathetic distress who, unable to bear the sight of her sick child, paces back and forth in the hallway. In the latter case, the mother may then end up with the common experience of burnout, which, in one U.S. study, beset about 60 percent of the 600 caregivers surveyed.

To further explore the mechanisms of empathy and compassion, Singer and Klimecki divided about 60 volunteers into two groups. One meditated on love and compassion, and the other experimental regimen trained participants to cultivate feelings of empathy for others. Preliminary results showed that after a week of meditation-based loving kindness and compassion, novice subjects watched video clips showing suffering people with more positive and benevolent feelings. The other subjects, who devoted a week to an experimental regimen that just cultivated empathy, experienced emotions that resonated deeply with others' sufferings. But these emotions also brought about negative feelings and thoughts, and this group experienced more distress, sometimes to the point of not being able to control their emotions.

A MEDITATION BENEFIT

Grow More Brain

Researchers from several universities explored whether meditation might bring about structural changes in brain tissue. Using magnetic resonance imaging, they found that 20 experienced practitioners of one type of Buddhist meditation had a greater volume of brain tissue in the prefrontal cortex (Brodmann areas 9 and 10) and the insula than a control group did (*graphs*). These regions play a role in processing attention, sensory information and internal bodily sensations. Future long-term studies will be needed to confirm this finding.



Aware of these destabilizing effects, Singer and Klimecki added training for the empathy group in compassion and loving kindness meditation. They then observed that this additional exercise counterbalanced the detrimental effects of training in empathy alone: negative emotions diminished, and positive emotions increased. These results were accompanied by corresponding changes in the areas of several brain networks associated with compassion, positive emotions and maternal love, including the orbitofrontal cortex, the ventral striatum and the anterior cingulate cortex. The researchers, moreover, were able to demonstrate that a week of training in compassion increased prosocial behavior in a virtual game specially developed to measure the capacity to help others.

SOURCE: "MEDITATION EXPERIENCE IS ASSOCIATED WITH INCREASED CORTICAL THICKNESS," BY SARA W. LAZAR ET AL., IN *NEUROREPORT*, VOL. 16, NO. 17; NOVEMBER 28, 2005

Illustration by David C. Killpack (brain)

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A DOOR TO CONSCIOUSNESS

MEDITATION EXPLORES the nature of the mind, providing a way to study consciousness and subjective mental states from the first-person perspective of the meditator. In a collaboration with expert Buddhist meditators at Wisconsin, we have studied the brain's electrical activity using electroencephalography during compassion meditation in which the meditators described the well-defined sense of self as becoming less fixed and permanent.

We found that these long-term Buddhist practitioners were able, at will, to sustain a particular EEG pattern. Specifically, it is called high-amplitude gamma-band oscillations and phase synchrony at between 25 and 42 hertz. The coordination of brain oscillations may play a potentially crucial role in the brain's building of temporary networks that can integrate cognitive and affective functions during learning and conscious perception, a process that can bring about lasting changes in brain circuitry.

High-amplitude oscillations persisted throughout the meditation for several dozens of seconds and gradually increased as practice progressed. These EEG traces differed from those of control subjects, in particular, in the lateral frontoparietal cortex. Changes in electrical activity may reflect an increased awareness in expert meditators of their surroundings and their internal mental processes, although additional research is needed to better understand the functioning of gamma oscillations.

Meditation brings about changes not just in well-defined cognitive and emotional processes but also in the volume of certain brain areas, possibly reflecting alterations in the number of connections among brain cells. A preliminary study by Sara W. Lazar of Harvard University and her colleagues showed that among longtime meditators, as compared with a control group, the volume of the brain's darker tissue, its gray matter, differed in the insula and prefrontal cortices—specifically, regions called Brodmann areas 9 and 10, which are frequently activated during various forms of meditation. These distinctions were most pronounced in older participants in the study, suggesting that meditation might influence the thinning of brain tissue that comes with aging.

In a follow-up study, Lazar and her colleagues also showed that mindfulness training decreased the volume of the amygdala, a region involved in fear processing, for those participants who showed the most noticeable reductions in stress over the course of training. Eileen Luders of the University of California, Los Angeles, and her colleagues further observed differences in meditators in the fibers called axons that connect different brain regions, suggesting an enhanced number of brain connections. This observation may support the hypothesis that meditation actually induces structural alterations in the brain. An important limitation of this research relates to the lack of long-term longitudinal studies that follow a group over the course of many years and to the absence of comparisons between meditators and people of similar backgrounds and ages who do not meditate.

Some evidence even exists that meditation—and its ability to enhance overall well-being—may diminish inflammation and other biological stresses that occur at the molecular level. A collaborative study between our group and one led by Perla Kaliman, now at the University of California, Davis, showed that one day of intensive mindfulness practice in experienced meditators turned down the activity of inflammation-related genes and altered the functioning of enzymes involved with turning genes on and off. A study by Cliff Saron of U.C. Davis looked at the effect of meditation on a molecule involved with regulating the longevity of a cell. The molecule in question was an enzyme called telomerase that lengthens DNA segments at the ends of chromosomes. The segments, called telomeres, ensure stability of the genetic material during cell division. They shorten every time a cell divides, and when their length decreases below a critical threshold, the cell stops dividing and gradually enters a state of senescence. Compared with a control group, the meditators who showed the most pronounced reductions in psychological stress also had higher telomerase activity by the end of the retreat. This finding suggests that mindfulness training might be able to slow processes of cellular aging among some practitioners.

A PATH TO WELL-BEING

ABOUT 15 YEARS OF RESEARCH have done more than show that meditation produces significant changes in both the function and structure of the brains of experienced practitioners. These studies are now starting to demonstrate that contemplative practices may have a substantive impact on biological processes critical for physical health.

More studies using well-defined, randomized controlled trials are needed to isolate meditation-related effects from other psychological factors that can influence the outcome of a study. Other variables that may affect study results are the level of motivation of a practitioner and the roles played by both teachers and students in a meditation group. Further work is needed to understand the possible negative side effects of meditation, the desirable length of a given practice session and the way to tailor it to a person's specific needs.

Even with the requisite cautions, research on meditation provides new insights into methods of mental training that have the potential to enhance human health and well-being. Equally important, the ability to cultivate compassion and other positive human qualities lays the foundation for an ethical framework unattached to any philosophy or religion, which could have a profoundly beneficial effect on all aspects of human societies. SA

Matthieu Ricard is a Buddhist monk who trained as a cellular biologist before he left France to become a student of Buddhism in the Himalayas about 40 years ago.

Antoine Lutz is a research scientist at the French National Institute of Health and Medical Research and also works at the University of Wisconsin–Madison. He has been a leader in studying the neurobiology of meditation.

Richard J. Davidson has pioneered the science of meditation as director of the Waisman Laboratory for Brain Imaging and Behavior and the Center for Investigating Healthy Minds at the University of Wisconsin–Madison.

MORE TO EXPLORE

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IN SEARCH OF THE OPTIMAL BRAIN DIET

The field of nutritional psychiatry is taking off as scientists home in on the ingredients for good mental health and cognitive staying power

By Bret Stetka

IN BRIEF

Research indicates that traditional diets from the Mediterranean, Scandinavia and Japan help to preserve our psychological and cognitive well-being.

These diets all feature fish, one of the best sources of omega-3 fatty acids—nutrients that play a vital role in promoting neuronal health and that may have helped drive the evolution of the human brain.

Studies indicate that diet changes may alleviate a range of psychiatric symptoms, and mental health practitioners may start to complement therapy and pharmaceutical treatments with recommended eating plans in the near future.

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CAROLYN FEELS GREAT THESE DAYS. SHE EXERCISES. SHE'S SOCIALLY active. She spends as much time with her four grandchildren as possible. But it wasn't always that way. A retired radiology film librarian from Pittsburgh, she began feeling apathetic and isolated seven years ago. "I'd just lost my mother, and my two sons had moved away," recalls Carolyn, now 75. She also struggled with excess weight, diabetes and chronic lung disease. She was grieving, eating a worrisome amount of junk food and slipping into what looked a lot like depression.

A few years later a friend told Carolyn about a depression-prevention study at the University of Pittsburgh. She signed up immediately. All 247 participants were, like her, older adults with mild depressive symptoms—people who without treatment face a 20 to 25 percent chance of succumbing to major depression. Half received about five hours of problem-solving therapy, a cognitive-behavioral approach designed to help patients cope with stressful life experiences. The rest, including Carolyn, received dietary counseling. Guided by a social worker, she discovered that she liked salmon, tuna and a number of other "brain-healthy" foods—which quickly replaced all the chips, cake and candy she was eating.

When the trial concluded in 2014, the results came as a surprise—to the researchers at least. The dietary counseling was not meant to have any substantial effect; Carolyn's group was the experiment's control. And yet psychiatrist Charles Reynolds and his colleagues discovered that both interventions had significantly reduced the risk of depression—by approximately the same amount. When they reviewed the data, all the patients scored on average 40 to 50 percent lower on the Beck Depression Inventory test, a common measure of depressive symptoms, 15 months after their sessions ended. What is more, only about 8 percent, regardless of the therapy they received, had fallen into major depression.

It cannot be ruled out that a placebo effect contributed to the improvements seen in both groups. Meeting with a health care professional and being proactive about getting better in and of itself may have helped participants feel more upbeat. In Carolyn's view, however, she had reversed her downward spiral largely by changing how she ate.

She is not alone in making that connection. Among scientists and clinicians there is a growing appreciation of the critical interplay between diet and brain health. The evidence is preliminary, and it is hard to tease out cause and effect. Perhaps people who eat well are also apt to have other healthy brain habits, such as regular exercise and good sleep routines. Or maybe depressed people tend to self-medicate with Oreos. But the data continue to accumulate. Every year the list of correlations between certain foods and mental well-being grows: fish and other sources of omega-3 fatty acids might help fend off psychosis and depression; fermented foods such as yogurt, pickles and sauerkraut seem to ease anxiety; green tea and antioxidant-rich fruits may help keep dementia at bay. And so on.

There is probably no single ingredient, no happy seed from the jungles of beyond, that is sure to secure a better mood or mental acuity into old age. But there do appear to be specific dietary patterns—calibrated by millions of years of human evolution—that boost our cognitive and psychological fitness. Within the nascent field of nutritional psychiatry, consensus is building about just what types of diets are best. And perhaps most exciting is the prospect that dietary intervention could serve as a

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ON THE MENU

Traditional Diets for Healthy Brains

Mediterranean

Research consistently finds the dietary patterns of cultures hugging the Mediterranean Sea to be among the healthiest in the world. Ingredients common to Greek, Italian, Spanish and Middle Eastern cuisine (*below*) are linked with improved cardiovascular, mental and neurological function.

Olive oil
Omega-3-rich fish (sardines, tuna, salmon)
Antioxidant-rich fruits and vegetables (tomatoes, peppers, eggplant)
Whole grains
Legumes
Moderate amounts of lean meat and red wine
Limited sugar and processed food

Okinawan

According to the World Health Organization, the Japanese have the highest life expectancy in the world—in part thanks to the population of Okinawa. Staples of the island group's traditional diet (*below*) include the nutrient-rich purple sweet potato, often eaten in place of rice. Indeed, Okinawans tend to eat less fish, meat, rice and sugar—and fewer calories overall—than do those in other parts of the country.

Antioxidant-rich vegetables (Okinawan purple sweet potatoes)
Seaweed
Some fish
Some meat
Limited sugar and white rice intake

Scandinavian

Swedish meatballs aside, Scandinavians cook, collect and cultivate a host of foods that together constitute the new Nordic diet, one of the world's healthiest. It is associated with reduced inflammation and decreased risk for cardiovascular disease and diabetes, both of which can influence brain health. Of particular note, Scandinavians tend to cook with canola oil, also called rapeseed oil, which contains far more omega-3 fatty acids than olive oil.

Fruits (lingonberries)
Vegetables (potatoes)
Nuts/whole grains (rye breads very common)
Seafood
Moderate amounts of meat and dairy
Canola (rapeseed) oil

valuable adjunct to medication and other therapies for mental disorders—just as it does in so many other areas of medicine.

GOOD DIET, BAD DIET

WHEN IT COMES TO PROMOTING brain health, the diet supported by the strongest data draws on traditional eating patterns from Italy, Greece and Spain. The so-called Mediterranean diet consists primarily of fruits, vegetables, nuts, whole grains, fish, lean meats in moderation, olive oil and maybe a little red wine. Earlier this year the first-ever randomized controlled clinical trial to test a prescribed diet to treat depression was published in *BMC Medicine*. The "SMILES" trial reported that after 12 weeks of consuming a Mediterranean-like diet, patients suffering from moderate to severe depression experienced significantly greater improvements on a commonly used depression symptom measure called the Montgomery-Åsberg Depression Rating scale (MADRS), compared with the control group. In 2011 public health expert Almudena Sánchez-Villegas of the University of Las Palmas de Gran Canaria and her colleagues assessed the relation between this diet and depression in more than 12,000 healthy Spaniards over the course of a median of six years each. They found that compared with people who did not eat a Mediterranean diet, those who did were significantly less likely to succumb to depression. For the subjects who followed the diet most closely, the risk dropped by a substantial 30 percent.

Sánchez-Villegas later confirmed the association in another large trial. The PREDIMED (Prevention with Mediterranean Diet) study—a multicenter research project evaluating nearly

ALAMY

EVIDENCE LINKS STEREOTYPICAL Western diets, which are heavy in processed and fatty foods, to higher rates of depression and anxiety. Unhealthy diets most likely contribute to a range of neuropsychiatric disorders by increasing inflammation.

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COLD-WATER FISH, such as salmon, tuna and sardines (*shown here*), are rich sources of DHA, a fatty acid that contributes to the growth, structure and function of nerve cells.

7,500 men and women across Spain—initially looked at whether a Mediterranean diet, supplemented with extra nuts, protects against cardiovascular disease. It does. But in 2013 Sánchez-Villegas and other investigators also analyzed depression data among PREDIMED's participants. Again, compared with subjects who ate a generic low-fat diet, those who adhered to the nut-enriched Mediterranean diet had a lower risk for depression. This was especially true among people with diabetes, who saw a 40 percent drop in risk. Perhaps these patients, who cannot adequately process glucose, benefited the most because the Mediterranean diet minimized their sugar intake.

Indeed, a central feature of the diet is that it is low in sugar, as well as processed foods and fatty meats, which are commonplace on most Western menus. Nutritional psychiatry researcher and SMILES trial lead author Felice N. Jacka of Deakin University and the University of Melbourne in Australia was one of the first to demonstrate an association between stereotypical Western diets and depression and anxiety. Most recently, she has drawn another link between poor diet and, quite literally, a shrinking brain. In September 2015 she and her colleagues discovered that older adults who consumed a Western diet for four years not only suffered higher rates of mood disorders but also had a significantly smaller left hippocampus on MRI scans. The hippocampus, composed of two seahorse-shaped arcs of brain tissue deep underneath our temples, is critical to memory formation. Jacka focused on the hippocampus because animal studies have also noted diet-related changes there.

A STUDY OF MORE THAN 12,000 HEALTHY SPANIARDS FOUND THAT THOSE WHO CLOSELY FOLLOWED A MEDITERRANEAN DIET HAD A 30 PERCENT REDUCED RISK OF DEPRESSION.

Scientists have proposed a number of possible mechanisms to explain this damage. Jacka's findings parallel other research revealing that high-sugar diets can prompt runaway inflammation and trigger a cascade of other metabolic changes that ultimately impair brain function. Ordinarily inflammation is part of our immune system's arsenal to fight infection and encourage healing, but when it is misdirected or overly aggressive, it can destroy healthy tissues as well. According to numerous studies, inflammation plays a role in a range of brain disorders—from depression and bipolar disorder to possibly autism, schizophrenia and Alzheimer's disease.

Two meta-analyses from 2010 and 2012 collectively reviewed data from 53 studies and reported significantly elevated levels of several blood markers of inflammation in depressed patients. And numerous studies have reported increased or altered activity of immune cells called microglia—which play a key role in the brain's inflammatory response—in patients with psychiatric disorders, including depression and schizophrenia. It is not clear whether inflammation causes mental illness in some cases, or vice versa. But the evidence suggests that many if not most known risk factors for psychiatric disorders, especially depression, promote inflammation; these include abuse, stress, grief and certain genetic predilections.

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By Land or by Sea?

Experts debate how human ancestors found enough fatty acids to build better brains

EVEN BEFORE EARLY HUMANS began foraging for seafood, they may have incorporated nutrient-rich fish from lakes and rivers into their diets, helping them to build healthy brains.

Omega fatty acids, including docosahexaenoic acid, or DHA, are key to brain health and most likely helped to drive the evolution of the modern human brain. But how did early humans access these vital nutrients? The answer is a matter of some debate.

For nearly two decades archaeologist Curtis W. Marean, associate director of Arizona State University's Institute of Human Origins, has overseen excavations at a site called Pinnacle Point on South Africa's southern coast, near where a newly discovered early human species, *Homo naledi,* was recently unearthed. His work there suggests that sometime between 195,000 and 123,000 years ago, during a glacial period known as Marine Isotope Stage 6 (MIS6), humans made a significant shift in their eating habits, moving from foraging for terrestrial plants, animals and the occasional inland fish to relying on the rich, predictable shellfish beds in the area.

Marean believes that this change occurred when early humans learned to exploit the bimonthly spring tides. And to do so, he says, our brains were already fairly well evolved. "Accessing the marine food chain could have had huge impacts on fertility, survival and overall health, including brain health," Marean explains, in part because of the high return on omega-3 fatty acids. But before MIS6, he speculates, hominins would have had access to plenty of brain-healthy terrestrial nutrition, including by feeding on animals that consumed omega-3-rich plants and grains.

Others disagree, at least in part. "I'm afraid the idea that ample DHA was available from the fats of animals on the savanna is just not true," says psychiatrist Michael A. Crawford of Imperial College London. "The animal brain evolved 600 million years ago in the ocean and was dependent on DHA and compounds essential to the brain such as iodine, which is also in short supply on land. To build a brain, you would need building blocks that were rich at sea and on rocky shores."

Crawford's early biochemical work focused on showing that DHA is not readily accessible from the muscle tissue of land animals. Using DHA tagged with a radioactive isotope, he and his colleagues also demonstrated that "ready-made" DHA—such as that found in shellfish—is incorporated into the developing rat brain with 10-fold greater efficiency than plant-sourced DHA.

Crawford's colleague and collaborator, physiologist Stephen Cunnane of the University of Sherbrooke in Quebec, also feels that aquatically sourced food was crucial to human evolution. But he believes that before MIS6, inland hominins had already incorporated fish from lakes and rivers into their diet for millions of years.

He suggests that it was not just omega-3s but a cluster of nutrients found in fish (including iodine, iron, zinc, copper and selenium) that contributed to our big brain. "I think DHA was hugely important to our evolution and brain health, but I don't think it was a magic bullet all by itself," Crawford says.

All three researchers are confident that higher intelligence evolved gradually over millions of years as mutations inched the cognitive needle forward, conferring survival and reproductive advantages. But advantages such as, say, figuring out how to shuck oysters—as well as track the spring tides—threw open the Darwinian floodgates. Cunnane comments: "Once we were able to access the coastal food chain in Africa—far more rich and reliable than inland sources of fish—brain and cultural evolution exploded." —*B.S.*

Jacka's work repeatedly points to traditional diets such as Mediterranean, Japanese and Scandinavian ones—all of which tend to be noninflammatory—as being best for our neurological and mental health. "There is no doubt that stress and uncomfortable emotions can cause us to reach for the biscuit tin—they don't call them comfort foods for nothing!" she admits. "But consistently the data show that the main constituents of a healthy brain diet include fruits, vegetables, legumes, nuts, fish, lean meats and healthy fats such as olive oil."

BRAIN-BUILDING FATTY ACIDS

INCREASINGLY, researchers are finding that the power of these more traditional diets extends beyond just supplanting bad food with good. In the summer of 2015 neuroscientists Amandine

EVERETT COLLECTION

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Pelletier, Christine Barul, Catherine Féart and their colleagues, all then at the University of Bordeaux in France, discovered that a Mediterranean diet may actually help physically preserve neuronal connections in the brain. They used a highly sensitive neuroimaging analysis technique called voxel-based morphometry to identify subtle changes in brain anatomy over time. And in September 2015 nutritional epidemiologist Martha C. Morris of Rush University and her co-workers reported that the MIND diet—a hybrid of the Mediterranean and the high-nutrient, low-salt DASH diet—may help slow cognitive decline and possibly even help prevent Alzheimer's. When they tested cognitive ability in 960 older adults, those who had followed the MIND diet for roughly five years achieved scores matching those of people 7.5 years younger.

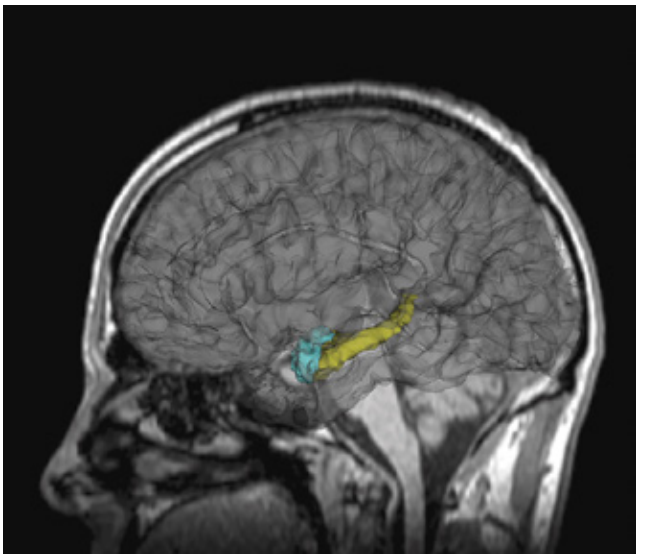
Our evolutionary backstory could explain these neuroprotective effects. Sometime between 195,000 and 125,000 years ago, humans may have nearly gone extinct. A glacial period had set in that probably left much of the earth icy and barren for 70,000 years. The population of our hominin ancestors plummeted to possibly only a few hundred in number, and most experts agree that everyone alive today is descended from this group. Exactly how they—or early modern humans, for that matter—managed to stay alive during recurring glacial periods is less clear. But as terrestrial resources dried up, foraging for marine life in reliable shellfish beds surrounding Africa most likely became essential for survival. Graduate student Jan De Vynck of Nelson Mandela Metropolitan University in South Africa has shown that one person working those shellfish beds can harvest a staggering 4,500 calories an hour.

The archaeological record corroborates the idea and indicates that our ancestors depended on a diet heavy in shellfish and cold-water fish—both rich sources of omega-3 fatty acids. These fats may have driven the evolution of our uniquely complex brains, which are 60 percent fat in composition. One omega-3 in particular, docosahexaenoic acid, or DHA, is arguably the single nutrient most strongly associated with brain health.

In 1972 psychiatrist Michael A. Crawford, now at Imperial College London, co-published a paper concluding that the brain is dependent on DHA and that DHA sourced from the sea was critical to mammalian brain evolution, especially human brain evolution. For more than 40 years he has argued that the rising rates of brain disorders are a result of post–World War II dietary changes—especially a move toward land-sourced food and, subsequently, the embrace of low-fat diets. He feels that omega-3s from seafood were critical to the human species' rapid neural march toward higher cognition [*see box on preceding page*].

Many studies have confirmed DHA's importance to the development, structure and function of the human brain: it is a component of neuronal cell membranes, facilitates neuron-to-neuron communication, and is also thought to boost levels of brain-derived neurotrophic factor, a protein that supports the growth and survival of brain cells. Given the starring role this and other omega-3 fatty acids play in shaping and maintaining our most complex organ, it makes intuitive sense that incorporating more of them into our diet—by emphasizing seafood—might, as the nutritional data suggest, protect the brain from going haywire. Also of note, DHA appears to decrease chronic brain-harming inflammation.

Fatty acids aside, there is another important link between our ancestors' diets, inflammation and mental health. As we evolved, the trillions of bacteria, fungi and other microorganisms that colonize our bodies and constitute the majority of our cells came along for the ride. This so-called microbiota—and its collective genes, the microbiome—makes a critical contribution to the formation and function of our digestion and immune system. A growing number of findings now suggest that disrupting it through poor eating habits comes at a cost to the brain.



IN BOTH ANIMAL AND HUMAN studies, typical unhealthy Western diets appear to cause damage to the hippocampus (*yellow on MRI scan*), a brain structure that plays an essential role in learning and memory. In one recent study, older adults who had consumed poor-quality diets over the course of four years had a smaller left hippocampus compared with peers who ate more healthfully.

COURTESY OF NICOLAS CHERBUIN

A BLOW TO THE GUT

IN ONE STRIKING (if slightly nauseating) experiment in 2014, then 23-year-old student Tom Spector wiped out about a third of the bacterial species in his gut by limiting his diet to McDonald's fast food. It took only 10 days. Spector played the guinea pig for two reasons: as a project to complete his genetics degree and to provide data for his father, Tim, a genetic epidemiology professor at King's College London, who studies how processed diets affect gastrointestinal bacteria. The Spector family's research did not assess specific health consequences—they were measuring only the drop in floral diversity in Tom's gut—but Tom did report feeling lethargic and down after days of burgers, fries and sugary soda. The decline in species was so drastic that Tim sent the results to three laboratories for confirmation.

Diet-induced shifts in the microbiota of the kind Spector brought on himself can rapidly ratchet up inflammation in the gut. On top of the ill effects just described, gastrointestinal inflammation can deplete our supply of serotonin, a neurotransmitter long tied to depression and other psychiatric disorders. About 90 percent of our serotonin is produced in the gut when certain microbes interact with cells lining the gastrointestinal tract (some microbes even produce a portion of our serotonin themselves). But by-products of inflammation convert serotonin's metabolic precursor, tryptophan, to a compound that

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generates neurotoxic metabolites linked with depression, schizophrenia and Alzheimer's.

The good news is that dietary changes can not only wreck our microbial diversity, they can boost it, reducing gastrointestinal inflammation in the process. In 2015 a group at the University of Pittsburgh conducted a study in which 20 African-Americans from Pennsylvania swapped diets with 20 rural black South Africans. In place of their usual low-animal-fat, high-fiber diet, the Africans consumed burgers, fries, hash browns, and the like. The Americans eschewed their normal fatty foods and refined carbohydrates for beans, vegetables and fish. After just two weeks the Americans' colons were less inflamed, and fecal samples showed a 250 percent spike in butyrate-producing bacterial species. Butyrate is thought to reduce the risk of cancer. The South Africans, on the other hand, underwent microbial changes associated with increased cancer risk.

"Dietary changes are the easiest way to alter your microbiome and help to control inflammation," says psychiatrist Emily Deans of Harvard Medical School. She believes diet is every bit as important as pills and psychotherapy in managing mental illness—a view informed by her own clinical practice. "I discuss nutrition with just about all of my patients," she adds, "and I think it can really help in managing conditions like depression, at least in some people." Deans also feels that timing of meals can influence mood, and research suggests that eating on a regular schedule can improve mental health.

Deans acknowledges that science has a long way to go before we fully understand the brain-diet relation. She is also wary of the massive probiotic industry that has, like the supplement industry in general, barreled ahead of the minimal but growing scientific evidence suggesting that probiotics might be effective in preventing or treating mental illness. "You can do studies with, for example, certain vitamins, and some might turn out positive and others negative," she explains. "But the truth is vitamins exist in all sorts of different chemical states in food and in just one state in supplements." This difference in form between nutrients in food versus pills explains why the data tend to favor nutrition through diet rather than supplementation. "I think we can safely say that certain dietary patterns seem to promote a healthy microbiome," Deans speculates, "like the Mediterranean diet and diets that include lots of fiber, fermented foods and fish." And a healthy microbiome may be essential for a healthy brain.

FOOD FOR THOUGHT

FOR SEVEN YEARS NOW Carolyn has been eating better—focusing on seafood and cutting back on sugar. She has lost weight, and her diabetes is under control. "It's part of a whole new way of life," she says, "knowing that what I eat can affect how I feel." That awareness is building momentum among patients and practitioners alike. In March 2015 a large team of clinicians and researchers published a report in the *Lancet Psychiatry* on behalf of the International Society for Nutritional Psychiatry Research—an organization Jacka co-founded in 2013. Citing modest therapeutic gains yielded by many psychiatric drugs, the authors called for the integration of nutrition-based approaches into mental health care. "The emerging and compelling evidence for nutrition as a crucial factor in the high prevalence and incidence of mental disorders," they wrote, "suggests that diet is as important to psychiatry as it is to cardiology, endocrinology, and gastroenterology."

Thanks to our evolutionary lineage (and plenty of fish), attention to our diets may prove critical to reversing the rising rates of mental illness around the world, lowering the proportion of people struggling with various forms of dementia, and staving off milder psychiatric symptoms and disorders. There is little doubt that eating right can help shuttle us through tough times—just as it may have done 160,000 years ago for a small group of humans huddled in coastal African caves.

DIET MAY BE "AS IMPORTANT TO PSYCHIATRY AS IT IS TO CARDIOLOGY, ENDOCRINOLOGY, AND GASTROENTEROLOGY," SAYS A 2015 REPORT IN THE *LANCET PSYCHIATRY*.

One of the leading proponents of leveraging diet to better brain health, Jacka is encouraged that interventional studies—in which patients are actually "prescribed" a particular diet and tracked over time, as they were in her own SMILES study—are finally getting under way. Such research will be able to offer more definitive proof of the connection between diet and mental and cognitive well-being.

More and more doctors and patients are beginning to see dietary interventions as a beacon of hope after several decades of disappointing psychiatric drug development. Too many patients suffering from mental illness or dementia do not respond adequately to existing medications, if at all. For example, selective serotonin reuptake inhibitors such as Prozac—one of the most commonly prescribed drug classes for treating depression—appear effective only in severe cases; they are often no better than placebo for mild to moderate disease. As scientists learn more about the pathologies behind mental and cognitive disorders, new and promising therapeutic targets will surely emerge. But it is clear that nutrition-based treatment plans—free from side effects and low in cost—will also figure prominently in the future of dementia and psychiatric care. SA

Bret Stetka is an editorial director at Medscape (a subsidiary of WebMD) and a frequent contributor to *Scientific American*. His writing has appeared in *Wired* and online for the *Atlantic* and NPR.

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THE FOR-REAL SCIENCE OF BRAIN TRAINING

Despite skepticism, research shows how cognitive exercises benefit cancer survivors, children with attention deficits, people with schizophrenia, and others

By Dan Hurley *Illustrations by Neil Webb*

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HAVE YOU HEARD THE NEWS? BRAIN TRAINING IS A SCAM: OVERHYPED AND understudied—a waste of time worse than Angry Birds.

That, at least, is the gist of news reports that ran in 2016, when the country's best-known brain-training company, Lumosity, was fined $2 million by the Federal Trade Commission (FTC) for making exaggerated claims in its advertisements. The FTC action came 15 months after the release of a statement from more than 70 neuroscientists who said they objected to unsubstantiated claims from the burgeoning brain-game industry. "Despite widespread claims, there is little evidence that brain-training games provide easy boosts to cognitive function," concluded an article by Simon Makin published in these pages in July 2015. "Making brain training look effective is easy because performance on the games inevitably gets better with practice."

But is that all there is to it? Does training on cognitive games result only in improvements on those games, as critics allege, with little evidence of meaningful real-world benefit? No young science is without controversy, and a number of studies by reputable scientists have indeed failed to find substantive cognitive benefits from such training. Yet shortly after the release of the "consensus" statement against brain training in 2014, more than 120 other scientists signed a response that cited 132 published studies showing that brain training does work.

No one is claiming that brain games will transform an average Joe into a Shakespeare or an Einstein. But there is plenty of evidence that computer-based cognitive training offers real benefits for certain populations. Most notably it can cut an older person's risk of having a car accident in half, mitigate the loss of basic cognitive abilities in people with schizophrenia, and improve the working memory of children who have attention deficits or are recovering from cancer. Quietly and persistently, outside the spotlight of news coverage, mainstream scientists at leading medical institutions around the world are building an ever stronger case for cognitive training targeted to such groups. Supported by the National Institutes of Health, the U.S. Naval Research Laboratory and other prominent funding organizations, they have published hundreds of randomized, placebo-controlled clinical trials in peer-reviewed medical journals.

These researchers worry that unjustified claims akin to those that drew the FTC's ire will tarnish the field and cause their own findings to be thrown out with the bathwater. "As an advocate and researcher for children who have, at this point, no other viable options, it's frustrating for me to hear the attacks on cognitive training," says psychologist Kristina K. Hardy, who works with childhood cancer survivors at Children's National Health System near Washington, D.C. (and who reports no financial connection with any brain-training company). "The science is promising. There's every reason to be optimistic about this approach."

AGING, INTERVENTIONS AND INDEPENDENCE

WE SHOULD FIRST get one thing straight: there is no evidence that cognitive training can prevent or slow the progression of Alzheimer's disease. Even for the condition known as mild cognitive impairment, often a precursor to Alzheimer's, the evidence is murky. But a new study, presented at a medical conference last summer, may change all those conclusions if its results pass muster in a scientific journal.

It should be noted that physical exercise—in particular, resis-

IN BRIEF

Companies offering brain training have recently come under intense scrutiny as scientists debate the degree to which the lessons learned benefit users.

But certain exercises allow people to practice and strengthen specific skills in ways that can improve day-to-day life. For instance, "useful field of view" training may help older drivers maintain the speed of processing needed to stay alert on the road and make them safer drivers.

Other tasks may help populations overcome handicaps that they face, as when working-memory training enhances cognition in childhood cancer survivors.

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tance training—has plenty of evidence showing it builds the brain as well as the body in older adults. And when you combine exercise with a healthy diet, ample social interaction and the use of brain games, as Finnish researchers did in a randomized controlled study published in 2015 in the *Lancet,* you get especially good results on cognitive function. But let's zoom in on the easiest intervention: computerized cognitive exercises that anyone can do and that may require as little as 10 total hours of practice.

Perhaps the most startling study in older adults, published in 2014, involved 2,832 volunteers in six cities across the U.S., whose average age was 73 when the research began. A team at Johns Hopkins University randomized the volunteers into one of three different types of cognitive training or into a no-contact control group. The training groups targeted memory, speed of processing or reasoning; each group tackled a series of tasks that essentially taxed those skills with progressively tougher challenges. Participants completed 10 one-hour sessions, followed in some cases by four booster sessions.

THE MOST EFFECTIVE TRAINING IN A STUDY OF OLDER ADULTS WAS ONE THAT DEVELOPED THEIR "USEFUL FIELD OF VIEW," A SKILL THAT MADE THEM SAFER DRIVERS.

The people who did memory training saw no benefit. (Go figure.) But those who had undergone training for reasoning or speed of processing did gain from the experience. A full 10 years later people in this group continued to outperform the control group on those functions. And tentative results presented in summer 2016 at the Alzheimer's Association annual meeting found that those who underwent some of the booster sessions were up to 48 percent less likely to be diagnosed with dementia 10 years later. Confirmation in a peer-reviewed journal could be a game-changer for the field.

The study, known as ACTIVE (*A*dvanced *C*ognitive *T*raining for *I*ndependent and *V*ital *E*lderly), found that the most effective computerized training was the one that targeted speed of processing, specifically a game challenging people's "useful field of view," or UFOV. For a brief blip of a moment, the player sees one of two similar-looking objects in the center of a computer screen and, simultaneously, a third object on the far edge of the screen. The challenge is to correctly identify which of the two objects was in the center and where exactly the object on the periphery was. Easy at the beginning, it becomes harder as the images flash by ever more quickly. Most everyone, however, gets more accurate at faster speeds over a period of days and weeks.

Psychologist Karlene Ball, now at the University of Alabama at Birmingham, first developed the task in the 1970s. In 2010 a study by Ball and her colleagues involving 908 older drivers found that 10 hours of training could cut the participants' rate of motor vehicle crashes in half for up to six years later. The training has also been shown to help drivers respond four tenths

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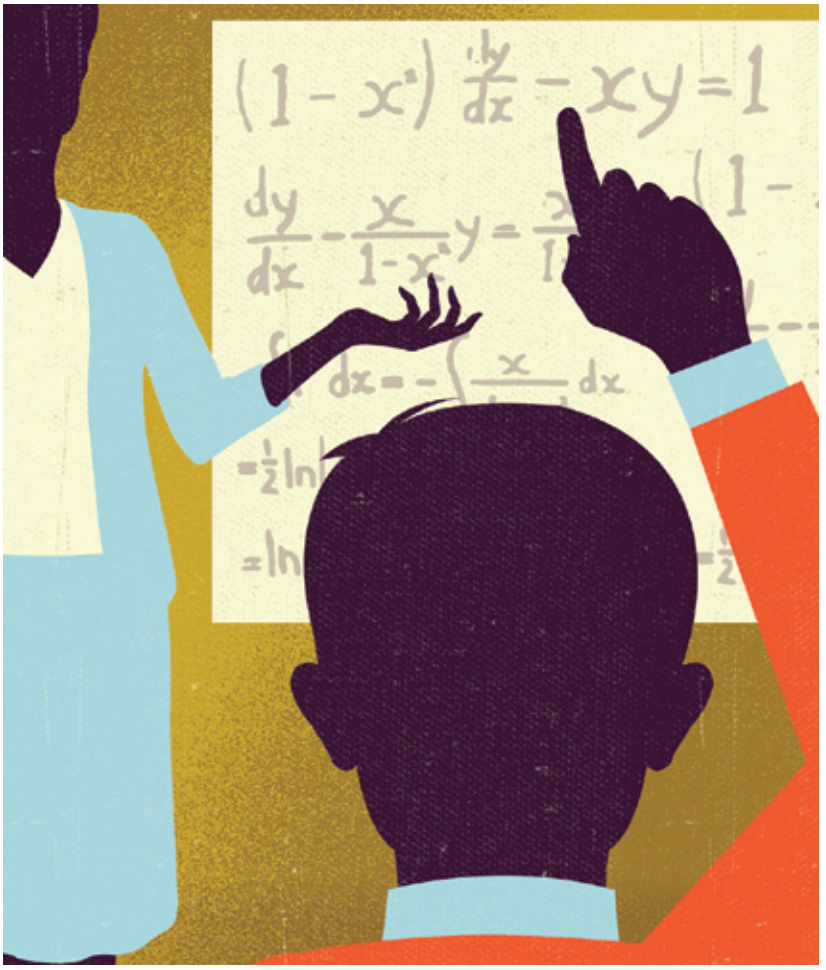

of a second faster in response to an unexpected obstacle. "I refer to that as the difference between seeing a deer cross ahead of you on the highway and seeing it crash through your windshield," says gerontologist Fred Wolinsky of the University of Iowa, who has collaborated on studies involving Ball's UFOV game.

The results have been impressive enough to gain the interest of the American Automobile Association and some car insurers, who are offering the training free or at a discount. "I've been working on this for the past 40 years of my life," Ball says. "I was very surprised that, first, we could get as much improvement as we did and, second, that it lasted for so long." Volunteers who participated in the same 10 hours of UFOV training, she found in a separate study, were also 30 percent less likely to exhibit symptoms of depression five years later.

Ball licensed the game in 2008 to Posit Science, a company co-founded by neuroscientist Michael Merzenich, formerly at the University of California, San Francisco. Customers can access versions of the game at www.drivesharp.com.

But UFOV games are not the only ones shown to improve, or at least preserve, cognitive abilities in older people. In November 2015 scientists at King's College London and their colleagues—using data from a six-month online experiment involving 2,912 adults older than 60—reported that participants randomized to training in reasoning or general cognitive skills showed enhanced performance on reasoning tasks that were different from the ones they had practiced. They also self-reported that they were better able to participate in essential activities of daily living. Most interestingly, there was a dose-response effect, so the more people trained, the better they did.

AFTER 10.5 HOURS OF WORKING-MEMORY CHALLENGES, CHILDREN WITH ADHD SHOWED MARKED IMPROVEMENTS ON OTHER, UNTRAINED MEMORY MEASURES.

WORKING-MEMORY WORKOUT

ANOTHER AREA of intense research is the use of computerized games for children and adults who have attention deficits. The games target working memory, which is the ability to maintain and juggle multiple items in your head—the cognitive equivalent of chewing gum while walking. You need working memory to recall the beginning of a paragraph even as you are reading the end or to do mental math. Working memory is essential for learning, reasoning and comprehension.

The strength of an individual's working memory was long believed to be a fixed trait until a small 2002 study by cognitive neuroscientist Torkel Klingberg of the Karolinska Institute in Sweden suggested it might be developed. He had children practice four tasks designed to stretch memory muscles, such as listening to a string of numbers or letters and then recalling them in reverse order. After a total of 10.5 hours of practicing games that put progressively tougher demands on their working memory, children diagnosed with attention-deficit/hyperactivity disorder (ADHD) showed improvements on other, untrained measures of working memory.

Since then, more than 200 studies of working-memory training have been published in the scientific literature about adults and children, healthy or diagnosed with ADHD and other conditions. Not all the studies have demonstrated benefits; a 2013 meta-analysis concluded that "current findings cast doubt on both the clinical relevance of working memory training programs and their utility as methods of enhancing cognitive functioning in typically developing children and healthy adults."

But a more recent, 2015 meta-analysis from a group of Dutch researchers found reliable evidence of gains for children and adolescents with learning disabilities. And a second 2015 meta-analysis of 12 previously published studies involving children or adults with ADHD or other work-

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ing-memory impairments found "persisting training benefits for inattention in daily life."

Klingberg's working-memory games are now offered by psychologists and other trained therapists through a program called Cogmed, owned by Pearson Education, an education and testing company based in London. (The cost varies depending on the therapist, but most charge fees between $1,500 and $2,000 for a full course of training.) Klingberg, who reports no current financial or other relationship with the company, says that although the effects on hyperactivity or impulsivity are nil, the program has been shown to reduce symptoms of inattention by roughly one third of a standard deviation. "That's pretty good," he notes. "We shouldn't expect miracles."

Pearson says it has no plans to seek approval from the U.S. Food and Drug Administration for its game as a treatment for ADHD, but both Posit Science and a Boston-based enterprise called Akili Interactive Labs have said they are working toward that goal. Akili's games are based on research by another U.C.S.F. neuroscientist, Adam Gazzaley. A pilot study presented in October 2015 at the American Academy of Child and Adolescent Psychiatry showed that their games were not only safe but engaging and helpful in improving attention, working memory and impulse control in a group of 80 kids with ADHD.

COMPARED WITH DRUGS AND PHYSICAL EXERCISE, COGNITIVE THERAPY MAY HOLD THE MOST PROMISE IN LIFTING THE MENTAL FOG OF "CHEMO BRAIN."

CANCER AND COGNITION

AFTER CHEMOTHERAPY FOR BREAST CANCER, many women report suffering the mental fog of "chemo brain," characterized by thinking and memory problems. A meta-analysis, published in October 2015 by researchers at Northwestern University's Feinberg School of Medicine, found that compared with other previously tested approaches such as drugs and physical exercise, "cognitive therapy protocols delivered after chemotherapy … hold the most promise." These protocols include the same kinds of approaches—aimed at improving verbal memory, attention and processing speed—that are offered by Cogmed and Posit Science.

Three other randomized trials, all using Cogmed, have found significant benefits for survivors of childhood cancer. The largest of the studies, led by neuropsychologist Heather Conklin of St. Jude Children's Research Hospital (who has no financial relationship with Cogmed), involved 68 survivors of either childhood acute lymphoblastic leukemia or brain tumor who had been diagnosed with cognitive deficits following treatment. The researchers assigned half the children, whose average age was 11, to do 25 training sessions on Cogmed at their homes, with weekly telephone coaching sessions. They put the other half on a waiting list to be trained after the study was completed. Compared with children on the waiting list, the

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kids who did the training significantly improved their performance on a host of cognitive tests.

Moreover, before-and-after exams showed that while subjects answered working-memory problems inside an MRI, two areas of their frontal lobes used less blood to solve problems after training than they had needed before—possibly because the engine on top of their shoulders had become more efficient. "These are kids who were developing more or less normally until they got cancer and received a treatment that changed the trajectory of their brain development," says Hardy, who collaborated on all three of the childhood cancer studies.

About 20 to 40 percent of children who survive leukemia experience long-term cognitive changes, she says, as do 80 to 100 percent of childhood survivors of brain tumors treated with radiation. "Working memory is one of the key abilities that changes in these children," Hardy says. "It changes early and leads to reductions in IQ and academic functioning over time. That's one of the reasons we are so excited about Cogmed. It specifically targets a neurocognitive domain that's among the first to be impacted in these children." She is now collaborating on two randomized trials aimed at preventing cognitive decline in childhood cancer survivors rather than merely trying to correct it after the fact.

SOCIAL TRAINING AND SCHIZOPHRENIA

HALLUCINATIONS AND DELUSIONS may be the most obvious symptoms of schizophrenia, but serious cognitive dysfunction is also commonly part of the picture, and antipsychotic medications do little to address it. Pioneering research by psychiatrist Sophia Vinogradov, now at the University of Minnesota, has shown that computerized cognitive training can make a major difference.

Partnering with Posit Science, Vinogradov and her colleagues have published more than two dozen randomized studies finding significant improvements in verbal memory, learning and daily functioning after training. Most of the studies have employed auditory training that might seem, at first glance, more fitting for people with hearing loss than for people with schizophrenia. "Sound sweeps," for instance, present a series of tones either rising or falling, like the sound of a siren approaching or receding. Laughably easy at a slow speed, they quickly become seemingly impossible to distinguish when played at, say, 12 milliseconds. Nonsense syllables are likewise presented at progressively faster speeds, with ever increasing levels of distracting background noise.

Vinogradov settled on such auditory challenges because people with schizophrenia are known to have basic defects in sensory processing, which are believed to underlie, at least in part, the defects in higher-level thinking skills long known to accompany the disease. Her studies have now demonstrated benefits in adults with established schizophrenia, in those with recent onset, and in adolescents and young adults at high risk for psychosis. "We definitely are seeing improvements in cognition, specifically with auditory training, where we see large gains in verbal cognitive operations," says psychologist Melissa Fisher, who collaborated with Vinogradov and is also now at Minnesota and has served as a consultant to Posit Science. "I don't think we have a definitive answer yet as to how much it is helping. But it's definitely promising."

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Equally promising and perhaps even more surprising are the benefits seen in early studies of computerized *social* training for people with schizophrenia, who often struggle with interpersonal relationships. A 2013 paper by Vinogradov and Fisher found that combining auditory training with computerized social training significantly improved scores on tests of social perception.

In 2014 they collaborated with psychologist Mor Nahum, director of research and development at Posit Science, on a pilot study involving SocialVille, a program designed to strengthen social cognition. "One exercise shows a person with facial expressions, and then you have to match it to the same expression afterward," Nahum explains. "A healthy adult might need to see this face for only 15 milliseconds to be able to correctly identify it afterward, whereas a [person with schizophrenia] needs much longer—orders of magnitude longer. The differences are striking. So they train to get better." After 24 hours of online game play from home or a clinic, people with schizophrenia significantly improved their performance on SocialVille and on standardized psychological measures of social cognition, social functioning and motivation.

PEOPLE WITH SCHIZOPHRENIA HAVE IMPAIRED SOCIAL COGNITION, INCLUDING SLOW PROCESSING OF FACIAL EXPRESSIONS. BRAIN TRAINING APPEARS TO HELP.

Now Nahum is working with Vinogradov, Fisher, and others on a four-site, randomized trial of SocialVille with 128 patients aimed at gaining FDA approval as a treatment for the social deficits associated with schizophrenia—a development that, if successful, would be a milestone in the field of computerized cognitive training. "Our goal is to move this out of the lab and into the community," Fisher says.

TO INCREMENTALITY AND BEYOND

RESEARCHERS SUCH AS FISHER insist that the cloud hanging over the field of cognitive training in the wake of the action against Lumosity has a silver lining. "In the short term," she says, "there has been concern that all cognitive training will be seen as fraudulent. But eventually I think it will be good for our field. Lumosity really did not have the research backing up their programs. But our group and many others do have strong evidence."

Scientists are also assessing several additional populations who could benefit from these training exercises. The SocialVille program, for instance, is now being studied as a means of strengthening the interpersonal skills of people with autism. A handful of studies have shown that computerized training can better the mental functioning of those with Parkinson's disease. A small-scale study involving 21 children with Down syndrome found that Cogmed boosted their short-term memory. Another study published in November 2015 concluded it could enhance working memory in children with epilepsy. And a third, published in February of the same year, indicated that such training has a long-term benefit in preschoolers who had been very low birth-weight babies. All these results need to be confirmed by additional and larger studies.

Should positive results continue to accumulate, the next step is to find a way to make computerized cognitive training affordable for those who could benefit from it. "Most people can't afford to pay $1,500 to $2,000 out of pocket for this intervention," Hardy says. "It already has as much evidence behind it as some of the drug-based interventions that are covered by insurance. There isn't an FDA approval for stimulant medications given to survivors of childhood cancers. Yet that certainly is covered by most insurance plans for these kids, and it is prescribed all the time."

And what about the great white whale of cognitive training: increasing intelligence in people with average or even above-average intelligence? Some academics who specialize in the study of IQ insist that improving it is a mission impossible. But that has not deterred the U.S. Office of the Director of National Intelligence from funding research into making intelligence analysts (read: spies) more, well, intelligent. Under the direction of the Intelligence Advanced Research Projects Activity, a program with the apt acronym "SHARP" (*S*trengthening *H*uman *A*daptive *R*easoning and *P*roblem-Solving) is now in its third year of sponsoring studies of computerized training and other methods, including physical exercise, mindfulness meditation and mild electrical stimulation of the brain.

Results from the SHARP program will likely be published in scientific journals later this year. "I don't want to steal the thunder of the research teams, and it's important to say that not everything worked," says neuroscientist Alexis Jeannotte, the program's manager, "but I will say that they have seen some small but significant gains in IQ. We really feel there's strong evidence for what they're seeing. They have tested interventions in literally hundreds of subjects in multiple sites."

Jeannotte's phrase "small but significant" is key. There are no shortcuts in the realm of human intelligence, no "limitless" brain boosters. We should be skeptical of anyone who promises them—particularly if they stand to make a profit. But there is good evidence to convince any skeptic that incremental and compounding improvement in cognitive function is achievable.

After all, our brain is clearly receptive to persistence and practice in education (just as negative events such as trauma or abuse hurt our cognitive abilities). Malleability is the defining attribute of the astonishing human brain. New studies of cognitive exercises and brain games—especially in vulnerable populations—underscore that. And that means, as Samuel Clemens might have put it, the reports of brain training's death have been greatly exaggerated. SA

Dan Hurley is a journalist who specializes in neuroscience, psychology and the social sciences. His latest book is *Smarter: The New Science of Building Brain Power* (Penguin Group/Hudson Street Press, 2013).

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BANKING AGAINST ALZHEIMER'S

Research has provided a host of clues to age-proofing our brains and making them more resistant to dementia

By David A. Bennett

I HAVE LOVED ARCHAEOLOGY SINCE MIDDLE SCHOOL AND HAVE SPENT MANY VACATIONS dragging my wife and kids around the world visiting ancient ruins—from the Anasazi kivas of the American Southwest to the "lost cities" of Machu Picchu and Petra to the big-headed Moai statues towering over Easter Island. Somewhere along the way, medical school and a neurology residency derailed my affair with the subject. But even now I sometimes imagine myself as a brain archaeologist—delicately picking through preserved specimens, cataloguing biological artifacts and trying to align my findings with people's unique histories. I am lucky to have had plenty of opportunity to indulge this daydream. At the Rush Alzheimer's Disease Center in Chicago, where I am director, about 100 scientists are searching for ways to treat and prevent a range of common neurodegenerative disorders. For nearly a quarter of a century I have led two longitudinal investigations—the Religious Orders Study and the Rush Memory and Aging Project—which have enrolled more than 3,350 older adults across the U.S. Our volunteers enter these studies, dementia-free, anywhere from their mid-50s to their 100s and, remarkably, agree to hours of testing each year. They undergo comprehensive physical examinations, detailed interviews, cognitive testing, blood draws and, in some cases, brain scans. Most important, all of them donate their brain after death to our research. The resulting collection fills various cabinets and two "freezer farms"—maintained at –112 degrees

CG imagery by Justin Metz

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Fahrenheit and protected by backup and alarm systems—covering about 4,000 square feet.

To date, we have conducted tens of thousands of clinical evaluations and more than 1,400 autopsies, generating an unprecedented set of data that we share with researchers around the world. Like archaeologists in the field, we sift through the remains in our care in hopes of understanding why some people stay sharp into their second century while others begin to lose their faculties as early as their 60s. We link risk factors and lifestyle choices to cognitive function and the biological footprints of disease. It is time-consuming work—the ultimate test of delayed gratification. You might think the more actual damage we find in the brain, the more cognitive challenges its owner experienced—and this is generally true. But not always. Sometimes, given two people with comparable amounts of brain injury, only one of them will have suffered ill effects [*see box on page 88*].

THE BRAIN IS THE MOST ADAPTABLE OF ALL OUR ORGANS. AS ALZHEIMER'S UNFOLDS, IT FIGHTS BACK, DRAWING ON COGNITIVE RESERVE.

In fact, it is rare to grow old with a completely healthy brain. Virtually every brain we examine exhibits at least some of the neuron-killing tangles associated with Alzheimer's disease, by far the most common cause of dementia. In about half, we find the scars of a previous stroke, big or small. And in almost a fifth, we discover so-called Lewy bodies—abnormal protein clumps that are the mark of Parkinson's disease and Lewy body dementia. But when we trace these laboratory finds back to each individual's records, we can account for only about half of the cognitive changes we measured on tests of memory, processing speed, and the like. Put another way: the pathology in someone's brain postmortem only partially tells us how well it functioned in the years leading up to the person's death.

The big question, of course, is, Why do some people develop symptoms of Alzheimer's dementia, and others do not? To a certain extent, genetics come into play; some people are unlucky to inherit high-risk genes associated with the disease. But investigators working with our data have also identified many key lifestyle factors that shape our brain's health into old age [*see box on page 90*]. Some—such as a healthy diet—probably help to slow the buildup of toxic materials that can cripple memory and critical thinking. For instance, Rush epidemiologist Martha Clare Morris has found that the so-called MIND diet—which is rich in berries, vegetables, whole grains and nuts—dramatically lowers the risk of developing Alzheimer's. She is now conducting a clinical trial of this diet.

But other life choices seem to actually bolster the brain's ability to cope with the disease, helping it compensate for any loss of mental firing power. In particular, we have found that the more engaged our volunteers stay throughout life—physically, socially and intellectually—the more resilient they are to dementia at its end.

We are beginning to understand exactly where this resilience comes from in some individuals, raising the hope that we might be able to prevent Alzheimer's in many more—or at least delay its onset so that death comes first. From the dawn of humankind until roughly half a century ago, death did typically come first; most of us did not live long enough to worry about neurodegenerative diseases. As life spans have lengthened, however, Alzheimer's has become increasingly prevalent and now affects more than five million Americans older than 65, or roughly one in nine. Diagnoses are forecast to triple by 2050. Our research suggests that we might be able to avert, or at least blunt, this looming crisis. Indeed, there are things we can all do—from childhood to our retirement years—to make our brain less vulnerable to the ravages of aging and disease.

LAYING FOUNDATIONS

ALZHEIMER'S WAS NOT ALWAYS such an urgent matter. My grandmother was born in October 1906, when people had more reason to worry about communicable diseases than age-related ones. A month after her birth, neuropathologist Alois Alzheimer presented a novel case of dementia to a meeting of his colleagues, who were so unimpressed that they did not ask a single question. The patient, a middle-aged woman named Auguste Deter, had not had syphilis, then considered a major cause of dementia. So instead Alzheimer attributed her symptoms to distinctive hard plaques he observed during autopsy between the nerve cells in her brain and odd tangles of fibers within the cells.

Today we know that these classic features are accumulations of malfunctioning proteins—mostly misfolded fragments of beta-amyloid in the plaques and abnormal tau in the tangles. For several decades after Alzheimer's discovery, though, the disease and its mysterious pathology remained largely forgotten. Then, between 1968 and 1970, neuropathologist Sir Bernard Tomlinson and his colleagues at Newcastle University in England ran a series of elegant studies that led to an important insight: older people without dementia often had plaques and tangles in their brain, too. Those with dementia just had more—and also suffered more strokes. The findings suggested that Alzheimer's disease might be far more common than anyone had realized.

Evidence for this began to accumulate. In April 1976 neurologist Robert Katzman, then at the Albert Einstein College of Medicine, penned a landmark editorial in the American Medical Association's *Archives of Neurology* in which he declared Alzheimer's disease a "major killer." The floodgates were opened, and a trickle of money began to flow into labs across the country. Between 1984 and 1991 the nascent National Institute on Aging funded 29 dedicated research centers, including our own. From the start, our primary interest was how to prevent Alzheimer's.

IN BRIEF

Several large longitudinal studies are offering important clues about how we can bolster our brain to better withstand the physical changes that come with aging.

Virtually all brains in old age contain some pathological signs of Alzheimer's disease, but only some people suffer any symptoms as a result. Those who do not develop dementia appear to have greater cognitive reserve to fall back on.

Choices we make throughout life—from learning a second language or studying music in childhood to finding purpose and remaining physically, intellectually and socially active in retirement—can build cognitive reserve and dramatically reduce the risk of developing dementia.

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Such efforts were in their infancy, but we hoped to take an original approach. Rather than limiting our investigation to the connection between potential risk factors and Alzheimer's dementia, as others were doing, we decided to also take into consideration the physical changes associated with aging and disease in the brain itself.

One big challenge was getting our hands on enough brains, especially from people *without* dementia. It is relatively easy to get organ donations from patients brought to an Alzheimer's clinic by concerned family members. Obtaining brains from healthy older people—who will also need to agree to multiple examinations before death—proves far more difficult. But we knew that nonsymptomatic people were a vital part of the puzzle. In a revealing 1988 study, Katzman performed autopsies on 137 former residents of a nursing facility, roughly half of whom had previously received an Alzheimer's diagnosis. Among the other half, though, he spotted 10 with significant Alzheimer's-related damage in the brain—who were also among the top-scoring residents on tests of cognitive performance. This group, Katzman noted, had higher brain weights and more neurons than the others with similar amounts of pathology. He proposed that maybe these people just had more brain to lose—an idea that sparked our interest in what is now referred to as neural or cognitive reserve.

How many more people like that were there? Could anyone bank this kind of mind-saving surplus? We planned our investigation to find out, taking inspiration from the Nun Study founded in 1986 by epidemiologist David Snowdon, now retired from the University of Kentucky. The Nun Study tracked nearly 700 members of the School Sisters of Notre Dame older than 75—a high percentage of whom donated their brain after death. Our plan was to complement, not copy, the Nun Study. With the help of the Chicago Archdiocese and the late Sister Katie McHugh, we networked with Catholic orders across the country. By 1993 we had secured funding to launch the Religious Orders Study, requiring organ donation for all participants at sign-up. Four years later we received additional funding to start the Rush Memory and Aging Project to study lay retirees.

We deliberately designed our experiment to be free from as many assumptions about aging and Alzheimer's as possible. For instance, there are no inclusion or exclusion criteria other than being old enough and agreeing to organ donation. We ask our participants not only about their diet, sleep and exercise—widely known to affect health and aging—but also about their education, musical training, foreign-language skills, personality, social activities, traumatic experiences, socioeconomic status as children, and more. We analyze how all these variables relate to changes in the brain and

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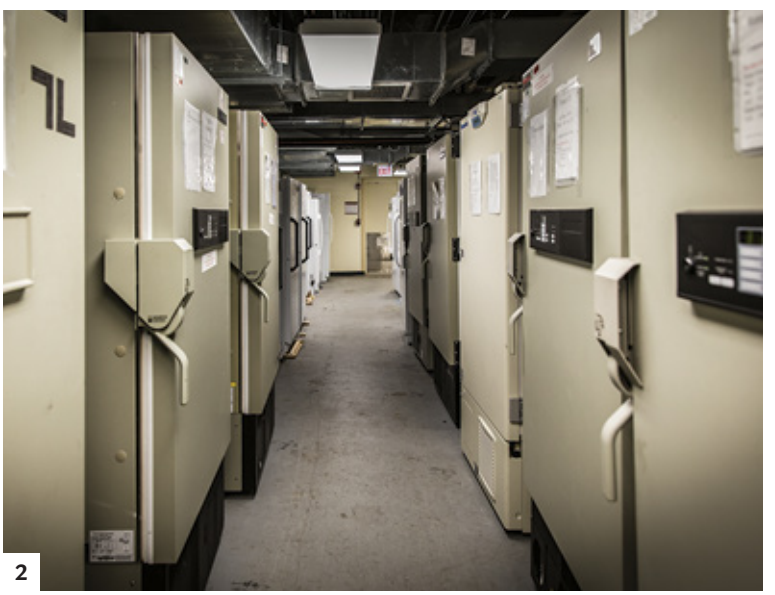
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FOR AROUND TWO DECADES Bennett (*1*) has led two large longitudinal investigations into Alzheimer's disease. All participants donate their brain after death. The collection, stored in specialized freezers (*2*), is yielding important clues about how to prevent the disease.

Photographs by Todd Winters

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symptoms of dementia, ignoring conventional diagnostic labels. We track how people's cognition changes, sometimes improving, but all too often declining. And we note the pace: some individuals run through the disease's course quickly, whereas others decline slowly or not at all. Our key question: How do you get into that latter group?

YOUR BRAIN FIGHTS BACK

MY GRANDMOTHER LIVED to be nearly 100 and liked to tell me repeatedly: "Aging isn't for sissies!" Given my professional focus on aging and dementia, she did not have to tell me twice. Clinically, Alzheimer's can be devastating. Over time it robs people of their memories, use of language, attention and independence. I often compare the deepening memory issues to losing pages from a chronological photo album of your life from back to front—with childhood memories the last to go. Ultimately sufferers lose the ability to function on any meaningful level. Mercifully, perhaps, many die from other conditions long before reaching the end stages of the disease. The good news is that as the disease unfolds, the brain fights back. Like all other systems in the body, the brain does not sit idly by, a mere bystander. In fact, it is the most plastic and adaptable of all our organs (which is how you learn in the first place). This plasticity appears to be a large part of what constitutes our reservoir of resilience or cognitive reserve.

To better understand it, we scrutinize the brains of people who seemed to have real cognitive staying power—or declined only slowly—despite the presence of plaques, evidence of stroke or other damage. Like Katzman, we find that such individuals tend to have more neurons—specifically in the locus coeruleus, a blue-tinted region in the brain stem normally involved in our stress and panic responses. The finding makes sense: most Alzheimer's patients eventually lose up to 70 percent of the neurons there. Working with psychiatrist William Honer of the University of British Columbia, we also discovered that slow decliners typically have higher amounts of specific proteins, such as vesicle-associated membrane protein, complexin-I and complexin-II, which help to relay messages across the synapses, or gaps, between brain cells.

Using our samples, neuroscientist Bruce A. Yankner of Harvard University discovered yet another protein that helps to actively preserve our mental abilities. Levels of this protein, called repressor element 1–silencing transcription factor, or REST, are highest in the brains of elderly people who live into their 90s and 100s. Perhaps not surprisingly, Yankner found in animal studies that REST protects neurons from death caused by oxidative stress or beta-amyloid, among other threats. His research shows that better cognition correlates with high levels of REST in the cortex

CASE STUDY

How Did Marge Stay Sharp?

I first met Marjorie Mason Heffernan in January 2003, when I began recruiting participants for the Memory and Aging Project at a retirement community, now called Presence Bethlehem Woods, in La Grange Park, Ill., a 40-minute drive west of Rush University. I am not sure what took us so long to enroll there; it is right next door to the Sisters of St. Joseph, our very first Religious Orders site, where we had been testing study participants for a decade.

Roughly a month after she signed up for our study, Marge—as she was known to friends and family—came in for her baseline evaluation. During the first week of March, I sat down to review the results with her. At 79 years old, she was doing great. On the Mini-Mental State Examination (MMSE), the most widely used test of overall cognitive abilities, she had scored a perfect 30. In fact, she performed extremely well on nearly all the 21 cognitive tests we gave her.

Over the course of seven years Marge proved to be an energetic study participant. She enrolled in a number of substudies—including a brain-imaging study and a behavioral economics and decision-making study. We evaluated her cognition eight times, and each time she scored a perfect 30 on the MMSE—apart from one test at age 80, in which she nearly scored 30, and one at age 84, when she dipped to 28. At the end of 2010, Marge died peacefully at home, at age 87, comforted by her son and two nieces.

SISTERS Betty Borman (*left*) and Marjorie Mason Heffernan (*right*) both participated in Bennett's study. Although his group found moderate signs of Alzheimer's in Marge's brain after death, she never showed any symptoms of dementia, consistently scoring high on tests of cognitive function.

COURTESY OF BETTY BORMAN

Like all our study participants, Marge had generously donated her brain for research. At autopsy, it weighed 1,246 grams, pretty much average for women. She had mild, widespread tissue loss, which is typical of Alzheimer's and other neurodegenerative diseases but can also be seen in healthy older brains. Under the microscope, her brain had enough beta-amyloid plaques and tau tangles to meet the pathological criteria for Alzheimer's. There were no signs of infarcts (areas of dead tissue that can indicate stroke) or Lewy bodies (marks of Parkinson's disease and Lewy body dementia). In short, the findings were consistent with moderate Alzheimer's, which raised the question: Why was Marge's cognition so good?

The answer might be found in her life story, which featured many of the factors that our studies indicate can boost cognitive reserve and hold dementia at bay. For one thing, she was well educated—having attended school for 22 years, a lot for a woman born in 1923. Her younger sister, Betty Borman, who joined our study after Marge's death, later relayed that both she and Marge graduated from Chicago Teachers College in the 1940s.

From the data we collected, I knew that

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and hippocampus, areas that are normally vulnerable in Alzheimer's. And when the investigators disabled REST in mice, the animals began to show signs of Alzheimer's-like neurodegeneration. Neurologist Aron Buchman in our group at Rush found that gene expression of brain-derived neurotrophic factor (BDNF) was associated with a slower rate of cognitive decline. Furthermore, it reduced the deleterious impact of Alzheimer's pathology on cognitive decline. In other words, for each unit of brain pathology, the effect on cognition was lower in persons with higher BDNF expression. This suggests that the increased expression is in response to the pathology. BDNF is well known to be involved in neuronal activity and synaptic plasticity in the brain.

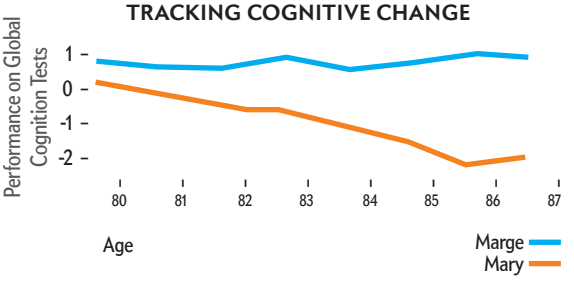
We and other researchers continue to search for additional biochemical factors that help save our mind as we age—plus other mechanisms that cause it harm. Recently neurologist Julie Schneider in our group at Rush uncovered that more than half of the brains in our collection contain abnormal clumps of the protein TDP-43, previously linked to frontotemporal lobe dementia and amyotrophic lateral sclerosis (Lou Gehrig's disease). Nearly 10 percent also bear scar tissue and a major loss of neurons in the hippocampus, critical to memory formation.

Others have observed signs of chronic inflammation in the brains of Alzheimer's patients, possibly supporting theories that tie the disease to infections such as human cytomegalovirus, which psychologist Lisa Barnes in our group confirmed is associated with lost cognition. And in collaboration with neurologist Steven Arnold, now at Massachusetts General Hospital, we found evidence of an association between Alzheimer's and abnormal insulin signaling in the brain.

This biological complexity has important implications for how we think about the treatment and prevention of this disease. With so many variables involved and likely many more to be discovered, it is not surprising that a lot of risk factors for Alzheimer's dementia are not actually related to Alzheimer's pathology. Working with neurologist Philip De Jager of Brigham and Women's Hospital, we recently examined the relation of more than 25 genomic variants linked to Alzheimer's dementia to several different types of abnormalities in the brain. We found that a few correlated with Alzheimer's pathology, but some were associated with other causes of dementia such as stroke, Lewy bodies and scarring in the hippocampus.

This complexity also means that it is exceedingly challenging—if not impossible—to single out meaningful targets for drug therapies. And given the imperfect correlation between brain pathology and cognitive performance, any interventions aimed at these biological processes would not necessarily have a large effect on symptoms. In fact, drug development for treating Alzheimer's has been slow and marked mostly by disappointment.

TRACKING COGNITIVE CHANGE



WHILE PARTICIPATING in the study, both Marge and another subject, Mary,* took annual tests of their cognition. Although the two women had similar levels of pathology, Marge's scores remained high and Mary's steadily declined.

Marge was cognitively and socially active. Betty later described her sister as a voracious reader, who could get through a book in a day. She told me that Marge founded a book club and that she and her late husband were involved in a local theater company. Marge also maintained a positive attitude, despite many adversities: she buried two of her three sons and two husbands.

Tests of Marge's personality and well-being backed up Betty's description. She had scored high on "purpose in life" and conscientiousness and low on neuroticism, anxiety, depressive symptoms and harm avoidance, a trait that encompasses shyness, excessive worrying and pessimism. Despite having a bad back, Marge was no homebody and scored the maximum possible in "life space"—a measure of one's geographical range—on our survey.

It is interesting to contrast Marge with another of our female participants, Mary.* She also enrolled at age 79 and, like Marge, completed eight annual clinical evaluations before her death at age 87. Mary's MMSE score at baseline was a solid 28 but declined to half that at her final evaluation. She was diagnosed with mild cognitive impairment at age 81, dementia at 84 and Alzheimer's at 85.

At autopsy, Mary's brain weighed 1,088 grams, much smaller than Marge's. And unlike Marge's brain, hers showed scarring from three small infarcts, although she had no history of strokes. But like Marge, Mary had mild tissue loss and enough damage to meet the pathological criteria for Alzheimer's. She actually had less beta-amyloid and fewer tangles than Marge did.

Despite having less Alzheimer's pathology than Marge, Mary suffered from a progressive loss of cognition, resulting in an inability to care for herself by the time of her death. Yes, she had a couple of small infarcts and some beta-amyloid in her blood vessels, and there may have been genetic differences that made Mary more vulnerable. But again, we found clues to her cognitive decline in her life story: Mary had 10 fewer years of education than Marge, having graduated only from high school. She scored low on measures of cognitive activity, purpose in life and life space. And she scored very high on harm avoidance, anxiety, neuroticism and depressive symptoms.

All efforts to develop therapies to prevent Alzheimer's have so far failed, but the comparison of these two women brings into focus the potential protective effects of life habits—ranging from early education to late-life social engagement. Marge and Mary had similar levels of Alzheimer's-related damage, yet their brains functioned at very different levels during their final years of life. —*D.A.B.*

COURTESY OF DAVID A. BENNETT

**Not her real name.*

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Building a Better Brain as We Age

Based on the results of scores of studies, here are 10 things you can do to reduce the risk of losing cognition and developing Alzheimer's dementia:

1. Pick your parents well! Make sure you get good genes, a good education, a second language and music lessons. Avoid emotional neglect.
2. Engage in regular cognitive and physical activity.
3. Strengthen and maintain social ties.
4. Get out and explore new things.
5. Chillax and be happy.
6. Avoid people who are downers, especially close family members!
7. Be conscientious and diligent.
8. Spend time engaged in activities that are meaningful and goal-directed.
9. Be heart-healthy: what's good for the heart is good for the brain.
10. Eat a MIND diet, with fresh fruit and vegetables and fish.
11. (For fans of *This Is Spinal Tap,* our list goes to 11.) Be lucky!

ROB MELNYCHUK *Getty Images*

BUILDING COGNITIVE RESERVE

AS RESEARCHERS CONTINUE to untangle the intricate web of disease mechanisms, it makes sense to focus on preventing Alzheimer's in the first place—to apply what we know about strengthening our brain to withstand the hits that come with aging. In our work, we have homed in on a variety of experiences, from childhood through old age, that can help us shore up cognitive reserve. Perhaps one of the most critical early steps toward ensuring better brain health is education—and not just formal schooling but other kinds of learning as well. Cognitive psychologist Fergus Craik and his colleagues have estimated that, on average, bilingualism delays the onset of dementia by as much as four years. And neuropsychologist Robert Wilson in our group at Rush has found that training in a second language, as well as in music—another form of language—correlates with a slower rate of cognitive decline. Had I only continued with those violin lessons!

That said, the relation between education and cognitive decline is complicated, as statistician Lei Yu in our group at Rush has discovered. In general, cognitive decline does not occur at a steady pace; it begins at one rate, and then, after a certain point, it accelerates. More education shifts this so-called change point later in life, maybe because more learning builds more brainpower to fall back on. Those with fewer years of formal education tend to have lower baseline abilities to start with and hit the change point sooner. Before the change point, both groups lose cognitive skills at roughly the same rate. Interestingly, even though those with more education typically start their descent at a later age, once they reach the change point they decline much faster. Biostatistician Charles Hall of the Albert Einstein College of Medicine has also identified this pattern in analyzing data from the Einstein Aging Study, an investigation of aging in the brain that has tracked a group of Bronx, N.Y., residents for more than three decades.

This precipitous downturn among the highly educated supports a theory called compression of morbidity, which James Fries, a professor of medicine at Stanford University, first put forth in 1980. Fries's basic hypothesis is that it is possible and desirable to delay the onset of diseases and compress the number of years someone spends ill and disabled at the end of life. For a disease such as Alzheimer's, being able to compress morbidity is hugely valuable, both emotionally and economically. This disease takes a terrible toll on both patients and family members, who are often put in the role of caregiver. Finding support is costly. Thus, any measure that can give someone even one more year of independent living translates into benefits not only for that person but for their family and the economy.

Among our participants, the more educated they are, the shorter, on average, their overall suffering. This trend explains a 1995 report by Yaakov Stern of Columbia University, which found that the risk of death among patients who have Alzheimer's dementia was greater for those with more education.

Education is not directly related to any neuropathology or protective neurobiology measured to date. Instead it seems to mute the effects of advancing disease on people's cognitive skills. The more damage someone has in the brain, the more protection he or she is afforded by extra years of education. This holds true at very high levels of education, as seen in our data, as well as at very low levels of education, as demonstrated by neuropathologist Jose Farfel of the University of São Paulo in Brazil.

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MINING THE GOLDEN YEARS

IF YOU DON'T PLAY the violin or speak another language, don't fret. Early educational experiences are not your only shot at building cognitive reserve. We have also found factors later in life that can buy more years of healthy living. Among them is something commonly called purpose in life, a measure of well-being that refers to our psychological tendency to derive meaning from life's experiences and to have clear intentions and goals.

Neuropsychologist Patricia Boyle in our group at Rush measured this trait in more than 900 participants in the Rush Memory and Aging Project, the majority in their 70s, 80s and 90s, using a scale based on the work of psychologist Carol D. Ryff of the University of Wisconsin–Madison. During up to seven years of follow-up, we discovered that those who scored higher on purpose in life were 2.4 times more likely to have avoided an Alzheimer's diagnosis, compared with those with lower scores. Relatively higher scores were also associated with slower rates of cognitive decline. In a similar analysis, Wilson found that higher levels of conscientiousness—one of the classic "big five" personality traits, characterized by organization, self-discipline, dependability and a drive to achieve—also offered some protection: participants in the Religious Orders Study scoring in the 90th percentile in conscientiousness had an 89 percent reduction in risk for developing Alzheimer's.

EDUCATION CAN HELP SECURE BRAIN HEALTH AS WE AGE. BILINGUALISM SEEMS TO DELAY THE ONSET OF DEMENTIA BY AS MUCH AS FOUR YEARS.

Psychological traits aside, other studies show that the size of our communities can affect how quickly Alzheimer's pathology encroaches on our cognition: among our participants, those with larger social networks are better able to postpone some of the worst symptoms. By social networks, we do not mean Facebook friends or Twitter followers but rather close relatives and friends with whom you can discuss private matters. Our first thought was that perhaps people with large social networks engage in more cognitive, physical and social activities, but controlling for these variables does not affect the association. Instead the protection from larger social networks might reflect in part the type of individuals who can form them. Simply put, they may have better developed people skills—and so a greater reserve of social cognition—to fall back on.

Physician Laura Fratiglioni, a professor at Sweden's Karolinska Institute, was first to describe the link between social networks and Alzheimer's in 2000. She based her findings on data from the Kungsholmen Project, a longitudinal population–based study on aging and dementia in Stockholm. Interestingly, she also measured how satisfied people were with their social contacts and found that frequent but unsatisfactory interactions with your children increase dementia risk. (It reminds me of an old Sam Levenson joke: "Insanity is hereditary—you get it from your children!")

All humor aside, Wilson in our group examined negative social interactions in a 2015 study, following 529 of our participants. All were symptom-free at the start of the study, but in keeping with Fratiglioni's finding, after an average of nearly five years, those who reported more neglect and rejection were more likely to show signs of cognitive impairment.

The central theme behind all these influences is positive engagement. We and many others have found that increases in cognitive, physical and social activities are all associated with a reduced risk of Alzheimer's dementia. Buchman in our Rush group went so far as to periodically place actigraph units (similar to pedometers) on the wrists of nearly 1,000 participants to measure their physical movements—capturing not just formal exercise but any activity, like playing cards or cooking. His results showed that those in the bottom 10 percent of intensity—the people who moved the least—were more than twice as likely to later be diagnosed with Alzheimer's, compared with the most mobile in the study. The implied lesson for us all: keep moving.

Another way to think about engaging with the world is to actually get out there. Epidemiologist Bryan James in our Rush group tested something referred to as life space among nearly 1,300 of our volunteers, none of whom showed signs of dementia at the start of the study. They measured the subjects' range during the previous week: Had they left their bedroom, front porch or yard? Had they ventured out of their neighborhood? Or had they made it farther afield and out of town? After about four years they found that those most constricted to their homes were twice as likely to develop Alzheimer's, compared with those with the largest life spaces—controlling for cognitive, physical and social activity. Is it the motivation to get up and go, or is it what you do when you get there?

We hope that in the years to come, as our collection expands and our means to study it grow ever more sophisticated, we will find many more clues to age-proofing our brain. When I used to visit my grandmother—we called her GG for "great grandmother"—at her retirement facility, she would always ask me, "So, David, still working on the Alzheimer's?"

"Yes, GG," I would answer. "Still examining old brains trying to figure out what protects us from memory loss."

She always followed with, "Find anything?"

"Sure," I'd say, "a little."

Then she'd lean over, point to a few people in her facility and whisper, "You better hurry up!"

How right she was. SA

David A. Bennett is director of the Rush Alzheimer's Disease Center in Chicago and is Robert C. Borwell Professor of Neurological Sciences there. He serves on numerous national and international advisory and editorial boards and has authored more than 600 peer-reviewed publications.

MORE TO EXPLORE

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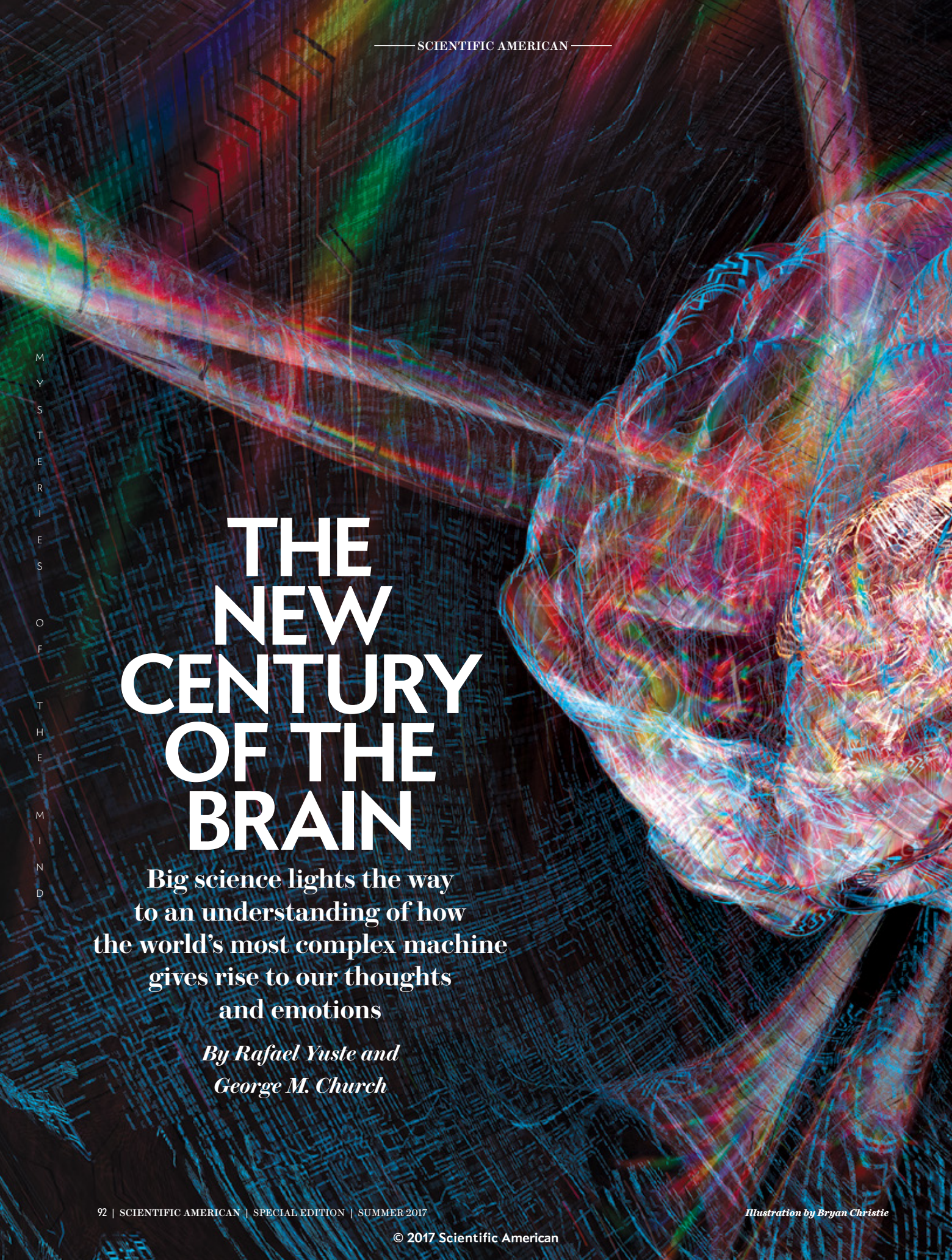

MYSTERIES OF THE MIND

THE NEW CENTURY OF THE BRAIN

Big science lights the way to an understanding of how the world's most complex machine gives rise to our thoughts and emotions

By Rafael Yuste and George M. Church

Illustration by Bryan Christie

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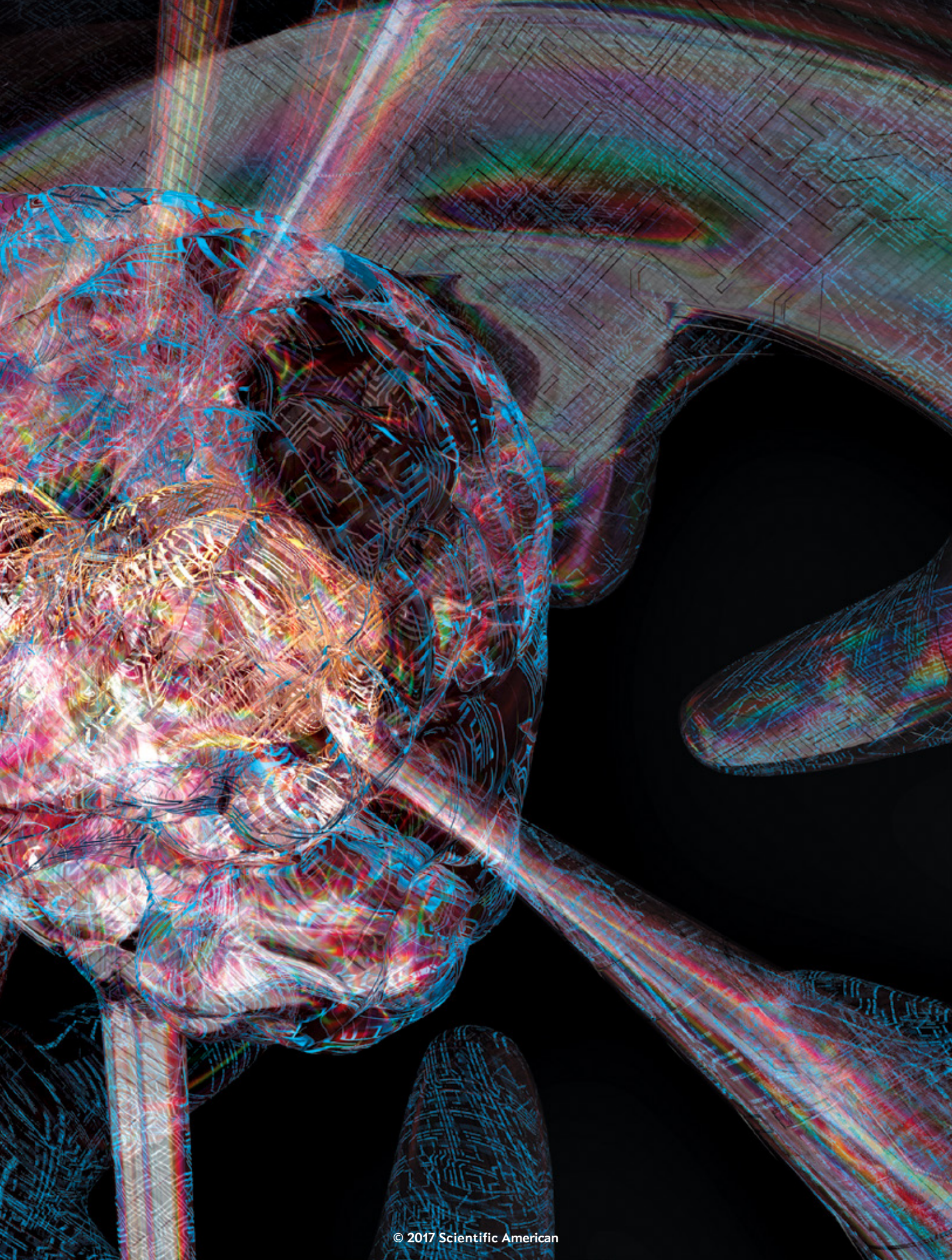

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DESPITE A CENTURY OF SUSTAINED RESEARCH, BRAIN SCIENTISTS REMAIN ignorant of the workings of the 1.4-kilogram organ that is the seat of all conscious human activity. Many have tried to attack this problem by examining the nervous systems of simpler organisms. In fact, almost 30 years have passed since investigators mapped the connections among each of the 302 nerve cells in the roundworm *Caenorhabditis elegans*. Yet the worm-wiring diagram did not yield an understanding of how these connections give rise to even rudimentary behaviors such as feeding and sex. What was missing were data relating the activity of neurons to specific behaviors.

The difficulty in establishing a link between biology and behavior in humans is still more acute. The media routinely report on scans showing that specific brain locations light up when we feel rejected or speak a foreign language. These news stories may give the impression that current technology provides fundamental insights into how the brain works, but that impression is deceiving.

A noteworthy example of the mismatch is a much publicized study identifying single brain cells that fired an electrical impulse in response to the face of actor Jennifer Aniston. Despite the hoopla, the discovery of a "Jennifer Aniston neuron" was something like a message from aliens, a sign of intelligent life in the universe but without any indication about the meaning of the transmission. We are still completely ignorant of how the pulsing electrical activity of that neuron influences our ability to recognize Aniston's face and then relate it to a clip from the television show *Friends*. For the brain to recognize the star, it probably has to activate a large ensemble of neurons, all communicating using a neural code that we have yet to decipher.

The Jennifer Aniston neuron also exemplifies the crossroads neuroscience has reached. We already have techniques to record the activity of single neurons in living humans. But to advance meaningfully, the field needs a new set of technologies that will enable investigators to monitor and also alter the electrical activity of thousands or even millions of neurons—techniques capable of deciphering what the pioneering Spanish neuroanatomist Santiago Ramón y Cajal called "the impenetrable jungles where many investigators have lost themselves."

Such breakthrough methods could, in principle, begin to bridge the gap between the firing of neurons and cognition: perception, emotion, decision making and, ultimately, consciousness itself. Deciphering the exact patterns of brain activity that underlie thinking and behavior will also provide critical insights into what happens when neural circuitry malfunctions in psychiatric and neurological disorders—schizophrenia, autism, Alzheimer's or Parkinson's.

Calls for a technological leap in studying the brain have started to be heard outside the laboratory. Indeed, the Obama administration announced in 2013 that it was establishing a large-scale initiative: the Brain Research through Advancing Innovative Neurotechnologies Initiative, or simply the BRAIN Initiative, the most visible big science effort of the president's second term.

The BRAIN Initiative, now in its third year and slated to last 15 years with several billion dollars of funding, targets development of technologies to record signals from brain cells in much greater numbers and even from whole areas of the brain. BRAIN complements other large neuroscience projects outside the U.S. The Human Brain Project, funded by the European Union, is a 10-year, $1.6-billion effort to develop a computer simulation of the entire brain. Ambitious neuroscience research projects are

IN BRIEF

The brain—and the way it gives rise to conscious thought—remains one of the great mysteries in all of science.

To better understand the brain, neuroscientists need new tools for analyzing the functioning of neural circuits.

Technologies that either record or control the activity of brain circuits may address these needs.

The Obama administration launched the BRAIN Initiative to promote development of these technologies.

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being launched in China, South Korea, Australia, Canada, Japan and Israel. The global consensus that is now propelling investment in brain science recalls other postwar science and technology initiatives focused on pressing national priorities: nuclear power, atomic weaponry, space exploration, computers, alternative energy and genome sequencing. The Century of the Brain is now upon us.

THE TV SCREEN PROBLEM

TRACKING HOW BRAIN CELLS compute the concept of Jennifer Aniston—or anything comparable that we encounter through subjective experience or perceptions of the outside world—is currently an insurmountable obstacle. It requires moving from measuring one neuron to gaining an understanding of how a collection of these cells can engage in complex interactions that give rise to a larger integral whole—what scientists call an emergent property. The temperature or solidity of any material or the magnetic state of a metal, for instance, emerges only from the interactions of a multitude of molecules or atoms. Consider carbon atoms. The same atoms can bond to create either a diamond's durability or the softness of graphite, which exfoliates so easily it forms words on paper. Whether hard or soft, these emergent properties depend not on the individual atoms but on the set of interactions among them.

WHAT IT TAKES TO PERCEIVE A FLOWER MAY ONLY BE DISCERNED BY OBSERVING THE ACTIVITY OF BRAIN CIRCUITS THAT PASS ELECTRICAL SIGNALS ALONG CHAINS OF THOUSANDS OF NEURONS.

The brain, too, most likely exhibits emergent properties that are wholly unintelligible from inspection of single neurons or even from a coarse, low-resolution picture of the activity of large groups of neurons. The perception of a flower or the retrieval of a childhood memory may be discerned only by observing the activity of brain circuits that pass electrical signals along intricate chains of hundreds or thousands of neurons. Although neuroscientists have long been familiar with these challenges, they still lack the tools to record the activity of the individual circuits that underlie a perception, or a memory, or that give rise to complex behaviors and cognitive functions.

One attempt to overcome this bottleneck involves assembling a map of the anatomical connections, or synapses, among neurons—an endeavor called connectomics. The Human Connectome Project, launched in the U.S. in 2012, will provide a structural wiring diagram of the brain. But, as with the roundworm, that map is only a starting point. By itself, it will be unable to document the constantly varying electrical signals that produce specific cognitive processes.

To make such a recording, we need wholly new methods of measuring electrical activity that go beyond existing technologies—which provide either a precise picture of the activity of relatively small groups of neurons or else sweeping imagery of large brain areas but without the resolution required to identify specific brain circuits switching on or off. Fine-scale recordings are made currently by inserting needlelike electrodes into the brains of laboratory animals to record the firing of a single neuron, the electrical impulse triggered after the cell receives chemical signals from other neurons. When a neuron is properly stimulated, the voltage across the cell's outer membrane reverses. This voltage shift induces membrane channels to usher in sodium or other positively charged ions. The inflow, in turn, produces an electrical "spike" that travels down the cell's long projection—the axon—spurring it to send a chemical signal of its own to other neurons and thus continue to propagate the signal. Recording from just one neuron is analogous to trying to follow the plot of a high-definition movie while viewing only a single pixel, making viewing all but impossible. It is also an invasive technique that can cause tissue damage when electrodes penetrate brain tissue.

At the other end of the spectrum, methods that track the collective activity of neurons across the whole brain are also inadequate. In the familiar electroencephalograph, invented by Hans Berger in the 1920s, electrodes sit on the skull and measure the combined electrical activity of more than 100,000 nerve cells underneath—the EEG records the oscillating "waves" of rising and falling amplitude over a few milliseconds, although it cannot resolve whether any individual neuron is active. Functional magnetic resonance imaging—producing the splotches of color illuminating active brain areas—records activity throughout the brain noninvasively but only slowly and with poor spatial resolution. Each image element, or voxel (a three-dimensional pixel), is a composite of about 80,000 neurons. Moreover, functional MRI does not track neuronal activity directly but records only secondary changes in blood flow within voxels.

To gain a picture of emergent patterns of brain activity, investigators need new sensing devices that can record from assemblages of thousands of neurons. Nanotechnology, with novel materials that sometimes measure less than the dimensions of individual molecules, may assist in making large-scale recordings. Prototype arrays have been built that incorporate more than 100,000 electrodes on a silicon base; such devices could record the electrical activity of tens of thousands of neurons in the retina. Further engineering of this technology will allow stacking of these arrays into three-dimensional structures, shrinking the electrodes to avoid damage to tissue and lengthening shafts to penetrate deep within the cerebral cortex, the brain's outermost layer. These developments could make it possible to record tens of thousands of neurons in a human patient while discerning the electrical properties of each cell.

Electrodes are only one way to track the activity of neurons. Methods that move beyond electrical sensors are making their way into the lab. Biologists, borrowing from technologies developed by physicists, chemists and geneticists, are beginning to visualize living neurons in awake animals going about their daily paces.

A hint of what might be in store came in 2013, when Misha Ahrens of the Howard Hughes Medical Institute's Janelia Research Campus in Ashburn, Va., used a larval zebra fish to perform microscopic whole-brain imaging. The zebra fish is one of

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neurobiologists' favorite organisms because the species is transparent in its larval state, allowing for easy inspection of the fish's innards, including the brain. In the experiment, the neurons of the zebra fish were genetically engineered to fluoresce when calcium ions entered the cell after it fired. A novel type of microscope illuminated the zebra fish brain by projecting a sheet of light over the entire organ while a camera took second-by-second snapshots of the neurons lighting up.

The technique used, called calcium imaging, which was pioneered by one of us (Yuste) to record the electrical activity of neural circuits, enabled the recording of 80 percent of the zebra fish's 100,000 neurons. It turns out that when the fish was at rest, many regions of the nervous system of the larval zebra fish switched on and off in mysterious patterns. Ever since Berger introduced the EEG, researchers have known that the nervous system is essentially always active. The zebra fish experiment gives hope that newer imaging technologies could help tackle a major challenge in neuroscience—the understanding of the persistent, spontaneous firing of large groups of neurons.

The zebra fish experiment is just the beginning because neuroscientists require still better technologies to discover how brain activity gives rise to behavior. New types of microscopes need to be designed to image simultaneously neuronal activity in three dimensions. In addition, calcium imaging operates too slowly to track the rapid firing of neurons and is also unable to measure the inhibitory signals that tamp down electrical activity in the cell.

Neurophysiologists, working side by side with geneticists, physicists and chemists, are trying to improve optical techniques that—instead of sensing calcium—record neuronal activity directly by detecting changes in membrane voltage. Dyes that alter their optical properties as voltage fluctuates—either deposited on the neuron or integrated through genetic engineering into the cell membrane itself—could improve on calcium imaging. This alternative technique, known as voltage imaging, may ultimately enable researchers to record the electrical activity of every neuron in an entire neural circuit.

Voltage imaging is still in its infancy, however. Chemists need to enhance the ability of the dyes to change color or other characteristics as a neuron fires. The dyes must also be designed to ensure that the chemicals do not damage the neuron. Already, though, molecular biologists are building genetically encoded voltage sensors; these cells read a genetic sequence to produce a fluorescent protein that is delivered to the cells' outer membrane. Once there such proteins can change the degree to which they fluoresce in response to alterations in a neuron's voltage.

As with electrodes, advanced nonbiological materials borrowed from nanotechnology may help. In place of organic dyes or genetic indicators, a new type of voltage sensor can be made of quantum dots—small semiconductor particles that exhibit quantum-mechanical effects and can be precisely tailored in their optical properties, such as the color or intensity of the light emitted. Nanodiamonds, another novel material imported from quantum optics, are highly sensitive to changes in electrical fields that occur as a cell's electrical activity fluctuates. Nanoparticles could also be combined with conventional organic or genetically engineered dyes to produce hybrid molecules in which a nanoparticle could serve as an "antenna" to amplify low-intensity signals produced by fluorescent dyes when a neuron is activated.

GOING DEEP

ANOTHER IMPOSING technical challenge to visualizing neuronal activity is the difficulty of delivering light to, and collecting it from, neural circuits deep below the surface of the brain. To solve this problem, neurotechnology developers are beginning to undertake collaborations with researchers in computational optics, materials engineering and medicine who also need to see through solid objects noninvasively, whether skin, skull or the inside of a computer chip. Scientists have long known that some of the light that hits a solid object gets scattered and that the scattered photons may, in principle, reveal details of the object from which it is reflected.

For example, the light from a flashlight on one side of a hand shines through, exiting as a diffuse glow yet without giving any clue about the location of the bones or vasculature underneath the skin. But information about the path the light takes through the hand has not been lost entirely. The disordered waves of light scatter and then interfere with one another. This light pattern can be imaged with a camera, and new computational methods can then reconstruct an image of what lies within—a technique used by Rafael Piestun and his colleagues at the University of Colorado Boulder to see through an opaque material. These methods might be combined with other optical techniques, including those used by astronomers to correct image distortions caused by the atmosphere's effects on starlight. So-called computational optics may help visualize the fluorescent glow from dyes that light up when subsurface neurons fire.

Some of these new optical techniques have already been used successfully to image the inner reaches of animal or human brains with a piece of the skull removed, enabling scientists to see more than a millimeter into the cortex. And with further refinement, these techniques might potentially offer a way to look through the thickness of the skull. But see-through optical imaging will not penetrate far enough to detect structures deep within the brain. Yet another recent invention may help address this problem. In a technique called microendoscopy, neuroradiologists currently insert a narrow but flexible tube into the femoral artery and then maneuver it to many parts of the body, including the brain, allowing microscopic light guides inserted in the tube to do their work. In 2010 a team at the Karolinska Institute in Sweden demonstrated an "extroducer"—a device that allows the artery or vessel through which the endoscope is threaded to be safely perforated, which makes any part of the brain, not just the vasculature, accessible for inspection by various imaging or electrical recording technologies.

Electrons and photons are the most obvious candidates for recording brain activity, though not the only ones. DNA technology could also play a critical role in a still distant future for monitoring neuronal activity. One of us (Church) has gained inspiration from the field of synthetic biology, which tinkers with biological materials as if they were machine parts. As research goes forward, lab animals could be genetically engineered to synthesize a "molecular ticker tape"—a molecule that changes in specific, detectable ways when a neuron becomes active. In one scenario, the ticker tape would be made by an enzyme called a DNA polymerase that starts off by continuously building a long strand of DNA that binds to another strand consisting of a preestablished sequence of nucleotides (the "letters" that are the building blocks of DNA). An influx of calcium ions, generated af-

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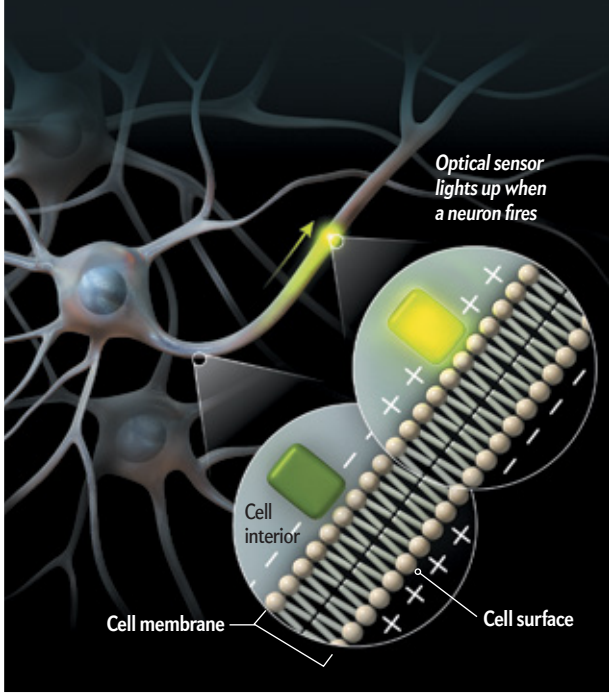
CELL MESSAGING

Listening In on Millions of Neurons

Neuroscientists need more efficient and less intrusive ways to observe brain circuits, in which electrical signals pass from one neuron to the next. A range of technologies—some in use, others just a glint in a researcher's eye—may enable scientists to record from thousands, even millions, of neurons. They will replace slow and imprecise methods that often require invasive electrical probes.

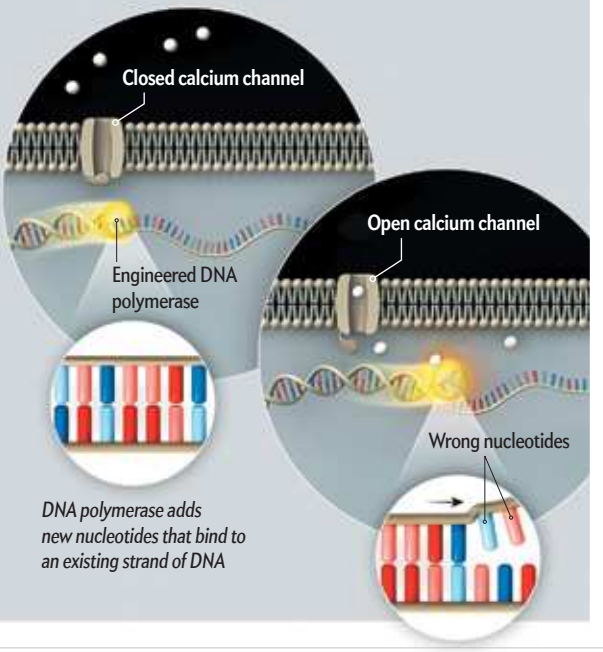
Voltage Imaging

This technique implants a dye into a neuron to determine if the cell is active. This sensor fluoresces when the electrical field across the cell membrane flips its charge as an electrical signal passes by. A detector (*not shown*) registers the event and may also monitor the activity of many other neurons, labeled with the same dye.



DNA Ticker Tape

A radically new approach—a molecular ticker tape—would, in one scenario, place a single strand of DNA with a known sequence of letters, or nucleotides, inside a cell but near its surface. An enzyme, DNA polymerase, would then add new nucleotides that bind to form a double-stranded molecule (*left*). When a neuron fires, an influx of calcium ions coming through a newly opened membrane channel would cause the enzyme to add the wrong nucleotides (*right*), an error that could be detected when the DNA strand is later sequenced.


Closed calcium channel
Open calcium channel
Engineered DNA polymerase
Wrong nucleotides
DNA polymerase adds new nucleotides that bind to an existing strand of DNA

ter the neuron fires, would then cause the polymerase to produce a different sequence of letters—in short, causing "errors" in the expected placement of nucleotides. The resulting double strand of nucleotides could be sequenced later from each neuron of the brain of an experimental animal. An innovative technique called fluorescent in situ sequencing would yield a record of different patterns of changes, the errors from the original ticker tape, corresponding to either the intensity or the timing of each of many neurons in a given volume of tissue. In 2012 the Church lab reported on the feasibility of this idea using a DNA ticker tape altered by magnesium, manganese and calcium ions.

Down the road, synthetic biology envisages the prospect of artificial cells acting as biological sentinels that patrol the human body. A genetically engineered cell could serve as a biological electrode, much smaller than a hair's width in diameter, that could be placed near a neuron to detect its firing. This pattern of firing could be recorded by a nanosize integrated circuit inside the synthetic cell—"electronic dust"—which could transmit the collected data by a wireless link to a nearby computer. These nanosize devices, a hybrid concoction of electronic and biological parts, might be powered by an external ultrasound transmitter or even from within the cell using glucose, adenosine triphosphate or another molecule.

TOGGLING ON OR OFF SWITCHES

TO UNDERSTAND WHAT IS HAPPENING in the brain's vast web of neural circuitry, researchers need to do more than just snap photographs. They must switch selected groups of neurons on or off at will to test what the cells are doing. Optogenetics, a technique widely adopted by neuroscientists in recent years, involves using animals that have been genetically engineered so that their neurons produce light-sensitive proteins derived from bacteria or algae. When exposed to light of a particular wavelength, piped in through an optical fiber, these proteins cause neurons to either switch on or shut down. Researchers have applied the technique to activate neural circuits involved in plea-

Illustrations by Emily Cooper

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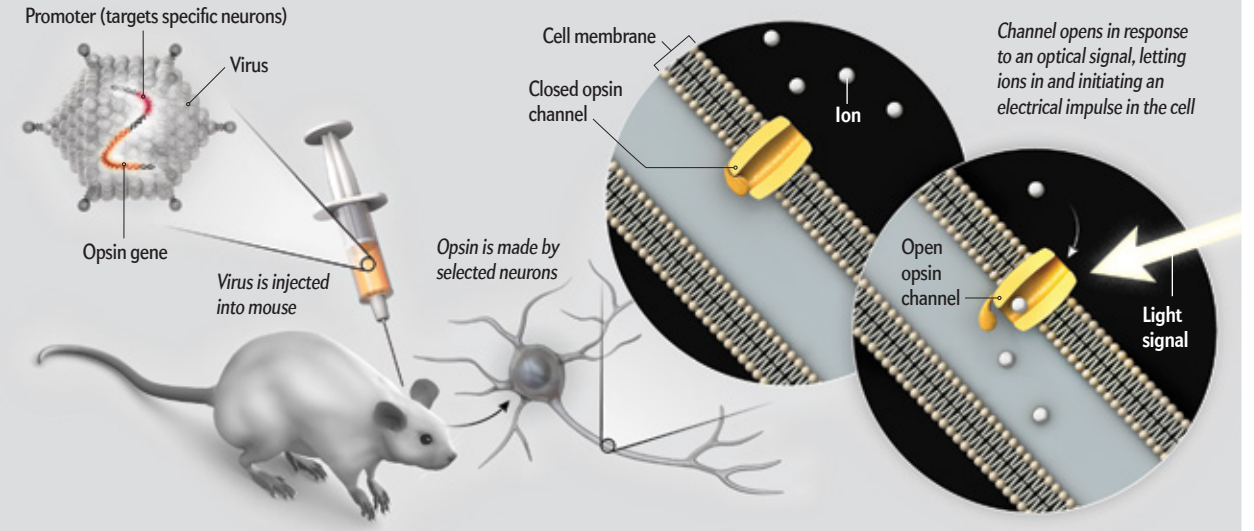
Installing a Neural Light Switch

Beyond observing electric currents flowing through circuits, neuroscientists increasingly want to turn individual circuits on and off at will so they can learn how to control specific forms of brain activity. One day these nascent technologies, two of which rely on optical signals, may quell epileptic seizures or parkinsonian tremors.

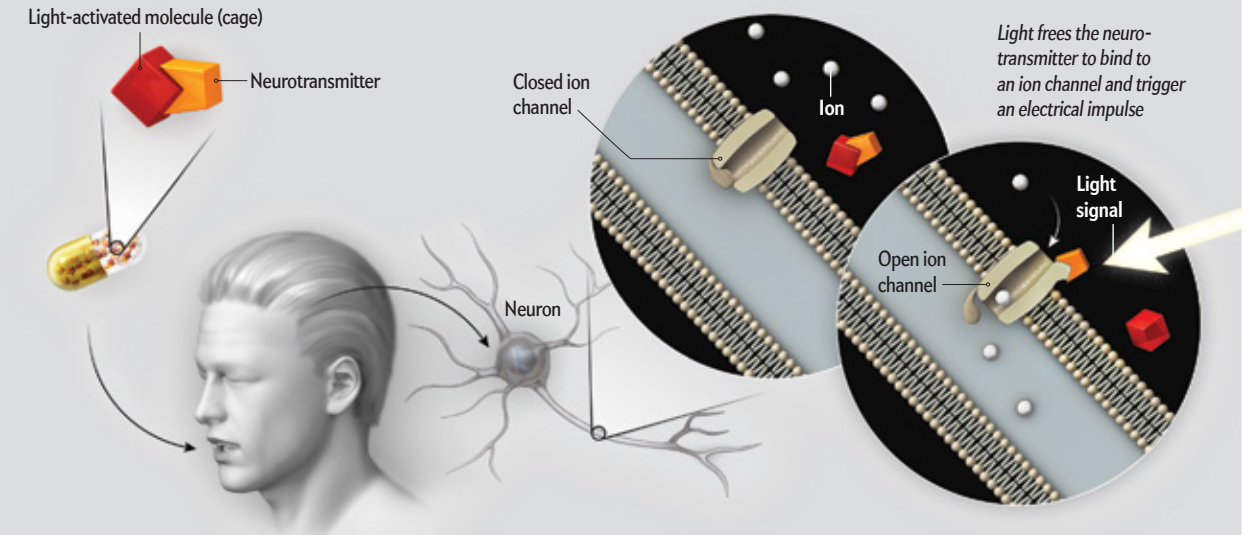
How Optogenetics Works

As the name implies, optical signaling and genetic engineering combine to activate a brain circuit in a living animal. First, a gene for a light-sensitive protein, an opsin, is placed inside a virus that, after injection into an animal, delivers the gene into neurons. Promoter DNA in the inserted genetic material ensures that only certain neurons make the opsin, an ion channel, and insert it in their surface membranes. A signal from an optical fiber inside a mouse skull opens the channel, allowing charged ions to enter the neuron and triggering a current through the cell.


Promoter (targets specific neurons)
Virus
Opsin gene
Virus is injected into mouse
Opsin is made by selected neurons
Cell membrane
Closed opsin channel
Ion
Channel opens in response to an optical signal, letting ions in and initiating an electrical impulse in the cell
Open opsin channel
Light signal

How Optochemistry Works

An alternative technique known as optochemistry avoids the need for cumbersome genetic engineering. A patient would first swallow a pill that contains a light-activated molecule—a cage—that attaches to a neurotransmitter, which regulates a neuron's activity. After the pill's content reached the brain, a pulse of light from an endoscope, or one delivered from outside the skull, would detach the neurotransmitter, which would go on to bind to and open a channel on the cell membrane that lets ions enter. The ions would then trigger the firing of the neuron, sending an electrical impulse traveling into the cell.



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sure and other reward responses and in the impaired movements characteristic of Parkinson's. They have even used optogenetics to "implant" false memories into mice.

The need for genetic engineering means that optogenetics may require lengthy approval protocols before it can be tested, or used as a therapy, in humans. A more practical alternative for some applications has been demonstrated by attaching neurotransmitters, the chemicals that regulate the activity of neurons, to a light-sensitive chemical called a "cage." Once exposed to light, the cage breaks apart, and the chemical escapes and becomes active. In a 2012 study, Steven Rothman, then at the University of Minnesota and in collaboration with the Yuste lab, placed ruthenium cages joined to GABA, a neurotransmitter that ratchets down neural activity, on the exposed cerebral cortex of rats that were chemically induced to produce epileptic seizures. Shining a pulse of blue light on the brain released the GABA and caused the seizures to abate. Similar "optochemical" approaches are currently used to probe the function of selected neural circuits. If further developed, they might serve as therapies for some neurological or mental disorders.

A long path still stretches from basic research to clinical applications. Each new idea for the large-scale measurement and manipulation of neural activity will have to be tested in fruit flies, roundworms and rodents before moving on to humans. An intensive effort could allow researchers to image and optically control a large number of the 100,000 neurons in a fruit fly brain within perhaps five years. Instruments to capture and modulate the neural activity of the brain of an awake mouse might not be possible for up to 10 years. Some technologies, such as thin electrodes to correct malfunctions in neural circuits in depressed or epileptic patients, could find their way into medical practice in the next few years, whereas some will take a decade or more.

As neurotechnologies grow in sophistication, investigators will need improved ways to manage and share enormous compilations of data. Imaging the activity of all the neurons in a mouse cortex could generate 300 terabytes of compressed data in an hour. But this is by no means an insurmountable task. Elaborate research facilities, akin to astronomical observatories, genome centers and particle accelerators, could acquire, integrate and distribute this type of digital data flood. Just as the Human Genome Project spawned the field of bioinformatics to cope with sequencing data, the academic discipline of computational neuroscience could decode the workings of entire nervous systems.

The ability to analyze petabytes of data will do more than bring order to floods of new information; it could lay the groundwork for new theories about how the cacophony of nerve firings translates into perception, learning and memory. The mega data analysis may also help confirm or dispel theories that could not be tested before. One intriguing theory postulates that the many neurons involved in the activity of a circuit develop particular sequences of firing known as attractors that may represent emergent brain states—a thought, a memory or a decision. In one study, a mouse had to make decisions about whether to traverse one section or another of a virtual maze projected on a screen. That action switched on dozens of neurons that exhibited dynamic changes in activity that resembled that of an attractor.

A better understanding of neural circuits could improve diagnosis of brain diseases from Alzheimer's to autism and give a deeper understanding of their causes. Instead of diagnosing and treating these conditions based on symptoms alone, doctors could look for specific alterations in the activity of particular neural circuits found to underlie each disorder and administer therapies to correct those abnormalities. By extension, knowledge about the roots of disease will likely translate into economic benefits for medicine and biotechnologies. As with the genome project, ethical and legal issues will need to be dealt with, particularly if this research leads to ways of discerning or altering mental states—outcomes that would necessitate careful safeguards for patient consent and privacy.

For the various brain initiatives to succeed, however, scientists and their backers must stay closely focused on the goal of imaging and controlling neural circuitry. The idea for the BRAIN Initiative grew from an article in the journal *Neuron* in June 2012. In it, we and our colleagues suggested a long-term collaboration among physicists, chemists, nanoscientists, molecular biologists and neuroscientists to develop a "brain activity map" derived by applying new technologies to measure and control the electrical activity of entire brain circuits.

We would urge that as the ambitious BRAIN project evolves, our original emphasis on tool building be retained. The scope of brain research is vast, and the BRAIN Initiative could easily devolve into a composite wish list that attempts to satisfy the broad-ranging interests of neuroscience's many subdisciplines. It could thus become nothing more than a supplement to already existing projects pursued by many individual labs working independently.

If this occurs, progress will be haphazard, and major technical challenges may never be met. We need collaboration among academic disciplines. Building instruments to image voltage in millions of neurons simultaneously throughout entire brain regions may be achieved only by a sustained effort of a large interdisciplinary team of researchers. The technology could then be made available at a large-scale, observatorylike facility shared by the neuroscience community. We are passionate about retaining a focus on new technology to record, control and decode the pattern of electrical spikes that are the language of the brain. We believe that without these new tools, neuroscience will remain bottlenecked and fail to detect the brain's emergent properties that underlie a virtually infinite range of behaviors. Enhancing the ability to understand and use the language of spikes and neurons is the most productive way to derive a grand theory of how nature's most complex machine functions. SA

Rafael Yuste is a professor of biological sciences and neuroscience at Columbia University and director of its NeuroTechnology Center. He is the 2013 winner of the NIH Director's Pioneer Award.

George M. Church is a professor of genetics at Harvard University and founder of PersonalGenomes.org, an open-access source for data on human genomes, neuroimaging, and behavioral and cognitive traits. He serves on *Scientific American*'s board of advisers.

MORE TO EXPLORE

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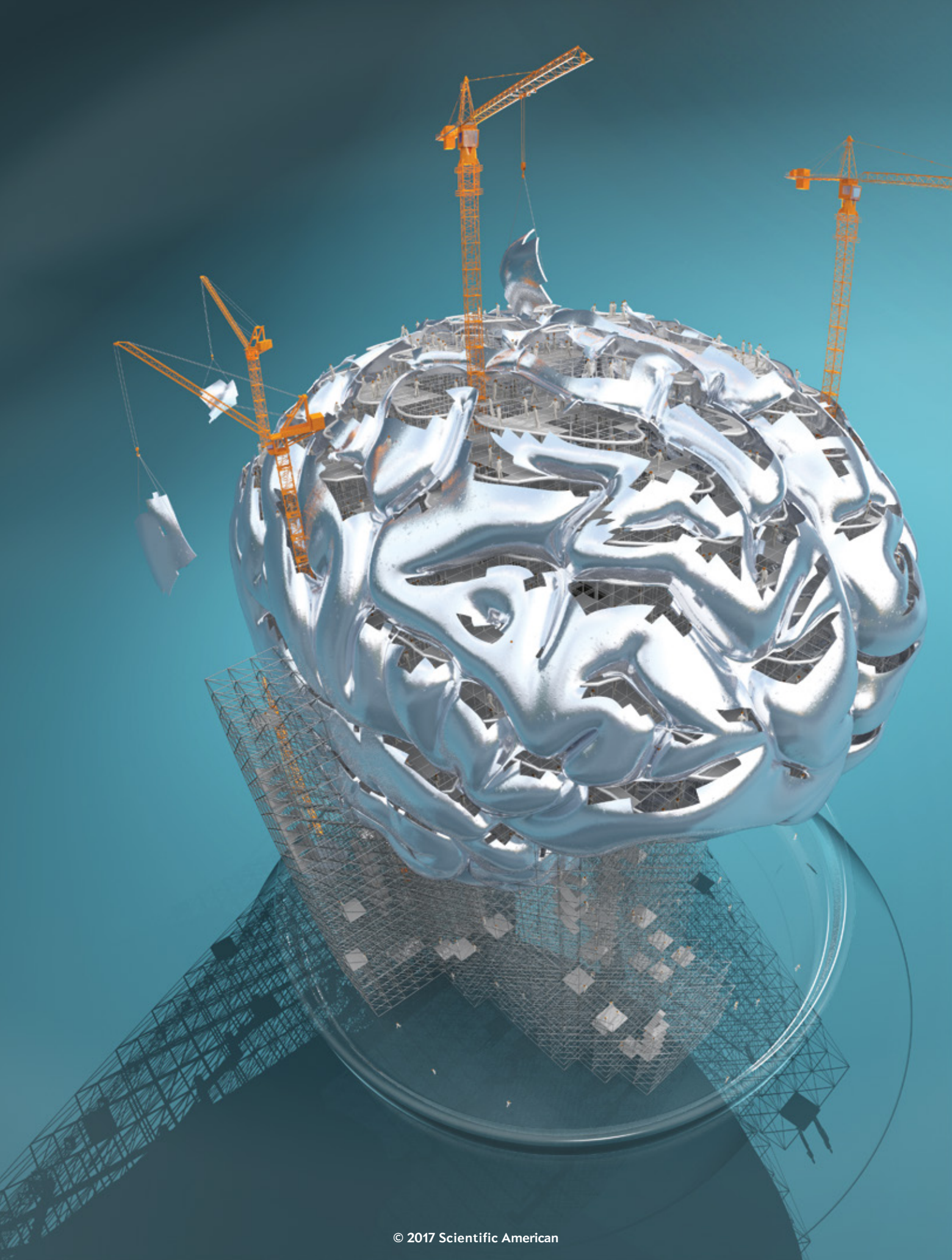

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"What I cannot create, I do not understand."

—Richard Feynman, 1988

LAB-BUILT BRAINS

Scientists copy nature's most complex organ in the hope of solving the mysteries of brain disorders, from autism to Alzheimer's

By Juergen A. Knoblich

Illustration by Bryan Christie

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EVERYTHING THAT MAKES US HUMAN IS LOCATED WITHIN 1.4 KILOGRAMS OF yellowish tissue composing the human brain. It is here that our thoughts develop, here that we feel love or hate, and where the most creative and most evil ideas of humankind arise. This walnut-shaped structure is also the most complex organ nature has generated. The brain harbors about 86 billion neurons, or nerve cells, that have to be born at the right time, migrate to the right place, and wire up in the right way if we are to survive and thrive.

Understanding exactly how the human brain develops and functions is the greatest challenge of modern biology. Most of what we have learned about the organ since the birth of neuroscience more than 100 years ago derives from experiments done on animals—frequently mice or rats. Scientists could justify this approach because mice and humans share a common brain architecture: they harbor many of the same types of nerve cells and rely on essentially the same parts of the brain to carry out shared mental processes. But humans and rodents differ in one key way. Whereas the mouse brain has a smooth surface, the human brain is highly folded.

To nonscientists, this difference might seem trivial. But neurobiologists believe that the folding makes a world of difference to human brain function. It allows for many more neurons to be placed within the same volume and is also a prominent feature of all "intelligent" animals, such as monkeys, cats, dogs and whales. Evolutionary biologists have shown that folding arose from another difference between mice and people: neurons in many parts of the brain arise from a specific set of precursor cells that exist only in minute numbers in mice.

Such differences may explain why many common genetic mutations responsible for severe neurological disorders in humans have little effect when bred into mice by researchers trying to study the mechanisms of human diseases. If the mutations affect the development or maintenance of proper human brain architecture or the functioning of cell types that are common only in humans, then the studies would be doomed to failure. In fact, the unique characteristics of the human brain may be one of the reasons that rodent studies have yielded no effective therapies for such brain disorders as schizophrenia, epilepsy and autism.

Recognition of the differences between mouse and human brains has spurred a hunt for more informative ways to conduct neuroscience experiments. Recently my laboratory has come up with an exciting approach: growing the largest part of the developing brain in miniature in a lab dish. These brain structures, called organoids, give neuroscientists a model of the human brain that should provide information they cannot obtain by running studies in mice. Researchers can observe what happens when the brain-in-a-dish, or mini brain, is exposed, for example, to the Zika virus, which can disrupt brain development in fetuses of infected women, or when an organoid is genetically engineered to mimic a brain afflicted with a neurological disease.

BRAIN-IN-A-DISH (SORT OF)

MY LAB BEGAN WORK on organoids in 2012, when Madeline A. Lancaster, then a postdoctoral scientist in the group, devised a way to replicate in a culture dish the essential processes that lead to brain formation in a human fetus during the first roughly 10 weeks of development [*see box on opposite page*]. Our procedure relies on human cells known as stem cells, which exhibit a remarkable feature called pluripotency. Pluripotent stem cells are the same type of cells found in the early embryo. When cultured under the right conditions, they can give rise to any kind of tissue, be it nerve, muscle, blood, bone or any other type. In the fetus, these new cells retain their pluripotency for only a few days. But using special lab cultures, researchers can preserve them in this state permanently and ultimately turn them into almost any desired cell type.

IN BRIEF

Knowledge about the human brain often derives from experiments performed on mice, rats or other animals. Brains of these species share much in common with the human organ, but they lack a highly folded surface, a difference that affects neural functioning.

Unique qualities of the human brain may help explain why rodent studies have failed to yield new treatments for brain disorders ranging from schizophrenia to Alzheimer's disease. That has spurred a search for new ways to conduct neuroscience experiments.

One alternative entails growing the largest part of the developing brain in a laboratory dish. These "organoids" most likely will give brain scientists information that cannot be obtained from mouse studies; they are already being used in investigations of the Zika virus.

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MANUFACTURING BRAIN PARTS

Grow Your Own

The technology that coaxes stem cells to develop into different types of biological tissue has now been used to grow a part of the brain that contains the cortex and other structures. It is also responsible for such higher mental functions as processing information from the outside world, forming memories and making decisions. To create such a mini brain, researchers give a tiny ball of cells nutrients and a bed on which to grow; then the cells recapitulate much of the developmental process that occurs in the early embryo.

1 The procedure begins with embryonic stem cells or induced pluripotent stem cells capable of turning into any cell type in the body. The latter cells can be derived from adult skin or blood cells that have been genetically altered.

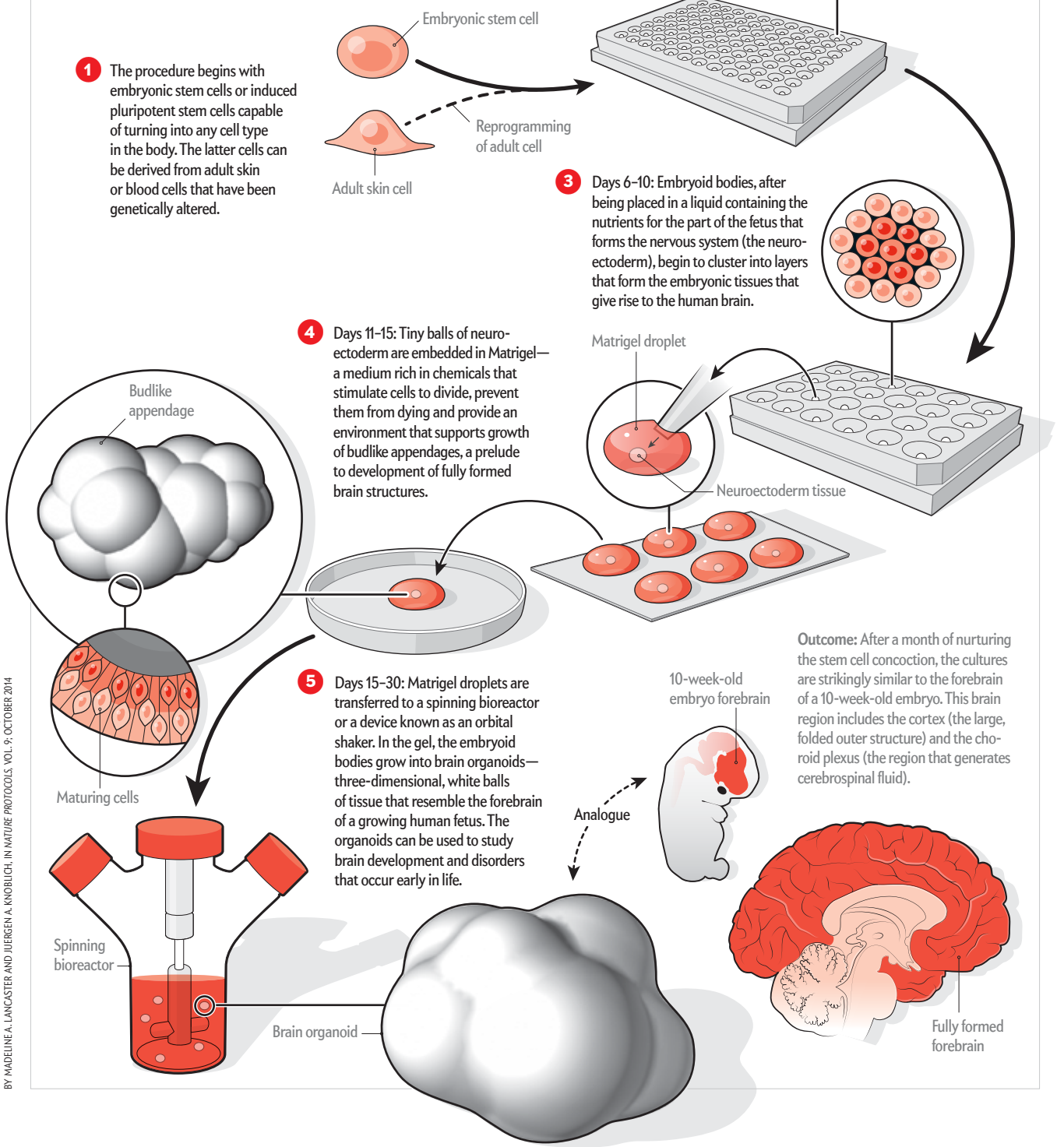
2 Days 0–5: The cells divide and aggregate into balls called embryoid bodies. Within three days, those cells start forming three distinct layers: ectoderm, mesoderm and endoderm.

3 Days 6–10: Embryoid bodies, after being placed in a liquid containing the nutrients for the part of the fetus that forms the nervous system (the neuroectoderm), begin to cluster into layers that form the embryonic tissues that give rise to the human brain.

4 Days 11–15: Tiny balls of neuroectoderm are embedded in Matrigel—a medium rich in chemicals that stimulate cells to divide, prevent them from dying and provide an environment that supports growth of budlike appendages, a prelude to development of fully formed brain structures.

5 Days 15–30: Matrigel droplets are transferred to a spinning bioreactor or a device known as an orbital shaker. In the gel, the embryoid bodies grow into brain organoids—three-dimensional, white balls of tissue that resemble the forebrain of a growing human fetus. The organoids can be used to study brain development and disorders that occur early in life.

Outcome: After a month of nurturing the stem cell concoction, the cultures are strikingly similar to the forebrain of a 10-week-old embryo. This brain region includes the cortex (the large, folded outer structure) and the choroid plexus (the region that generates cerebrospinal fluid).



SOURCE: "GENERATION OF CEREBRAL ORGANOIDS FROM HUMAN PLURIPOTENT STEM CELLS," BY MADELINE A. LANCASTER AND JUERGEN A. KNOBLICH, IN *NATURE PROTOCOLS*, VOL. 9; OCTOBER 2014

Illustration by Tami Tolpa

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To start, we culture the cells in a liquid containing all the nutrients needed for growing the neuroectoderm, the part of a fetus that forms the nervous system. When the cells aggregate into a ball called an embryoid body, we embed the ball in an amazing substance called Matrigel. This gel, produced by cultured cells that were isolated from a mouse cartilage tumor, resembles the membrane on which cells sit in the fetus. Matrigel, which is rich in factors that both stimulate cells to divide and prevent them from dying, provides a scaffold that is stiff enough for cells to grasp but malleable enough to be modified by the cells, which in turn alter its shape.

The outcome of these experiments has been truly spectacular. Left to their own devices in the gel, the embryoid bodies grow into three-dimensional, white balls of tissue that resemble the embryonic human brain. Exposed to the proper chemical signals that trigger fetal brain development, stem cells grow into exact replicas of the human forebrain, the region responsible for higher mental functions. It includes such components as the cortex (the large, folded outer structure) and the choroid plexus (the region that generates cerebrospinal fluid). We also find other structures that guide cells to their proper place in the developing brain. The medial and lateral ganglionic eminences, which perform this function, assist in giving rise to cells that generally tamp down neural activity (interneurons) and the hippocampus, which is involved in memory formation.

ORGANOIDS DERIVED FROM STEM CELLS HAVE ALREADY AIDED RESEARCH ON THE ZIKA VIRUS.

Cells in a growing organoid arrange themselves identically to those in the brain of an eight- to 10-week-old human fetus. In rare cases, the organoids even grow small eyecups, indentations in the tissue that contain colored pigments, much as occurs when the human eye begins to form. Also, as happens in a developing brain, the cells divide and give rise to the kinds of nerve cells found in an embryo. And the nerve cells send out axons—long cables that make contact with other neurons to form an active signaling network. Before forming these networks, the neurons migrate from one area to another, much in the way they do in the fetus, potentially providing clues to what happens when neurons end up in the wrong place, as they often do in psychiatric disorders.

ON THE SHOULDERS OF GIANTS

BUILDING TISSUES in culture is not really a new idea. As with most scientific discoveries, the current organoid boom relies on years of pathfinding research, some of it dating back more than a century. Already in 1907 zoologist Henry Wilson had demonstrated that certain lower animals, such as sponges, can put themselves back together after being broken up into single cells, an indication that the brain is endowed with a program for assembling its myriad parts.

In 1939 Johannes Holtfreter discovered that the various cells in a frog embryo will seek one another out and regenerate their shape even after they have been completely separated. During the 1980s this finding led to a huge boom in "reaggregation" studies, in which complex animal organs such as the retina and even the cortex were formed in the lab by bringing together their diverse cell types.

Building on early reaggregation experiments conducted from 2006 to 2010, the late Japanese scientist Yoshiki Sasai of the RIKEN Center for Developmental Biology pioneered the use of pluripotent stem cells for growing nervous system tissue, most notably the human retina. In fact, our brain organoid technology merged his techniques with groundbreaking work by Hans Clevers of Utrecht University in the Netherlands, who combined stem cells with Matrigel to establish a culture system that can be used for growing gut, stomach, and even liver and pancreatic tissue.

Beyond drawing lessons from these earlier studies, our work makes use of recently developed technologies that are dramatically turning the entire field of biomedical research upside down. One called reprogramming was developed by Japanese Nobel Prize laureate Shinya Yamanaka of Kyoto University. Through a simple set of genetic manipulations, reprogramming turns fully matured body cells back into pluripotent stem cells—and it can do so for virtually any cell, from skin to blood cells. Stem cells from a sample of skin or blood can then be transformed into various types of brain cells, and those cells can then be grown into organoids. The approach can thereby avoid the need to use cells derived from embryos.

Reprogramming allows an organoid grown from the cells of a patient with a genetic disorder to be compared with ones from a healthy individual to ferret out underlying causes of a disease because the genetic defect in the patient's cells should afflict the organoid much as it affects the developing fetus. In fact, we have already used the organoid technology to gain insight into microcephaly, in which patients are born with a brain of severely reduced size. We found that organoids grown from cells of a patient with microcephaly are much smaller than normal. Because we can grow the patient's cells in unlimited numbers, we can now undertake detailed analyses of the chain of molecular events that leads to microcephaly in a developing fetus. Much the same should be true for other brain disorders: using patients' cells to grow organoids may enable neuroscientists to better understand the defects in brain formation that underlie schizophrenia, epilepsy and other diseases that are difficult or impossible to study in animals.

Organoids derived from the reprogrammed cells of individuals who are not ill can also be useful. Indeed, they were put to good use during the 2015–2016 Zika epidemic, which has been found to cause microcephaly in a number of babies born to women infected during pregnancy. Multiple labs working on organoids, first in Brazil and then in the U.S., established that the virus can lead to microcephaly—a link that would have remained hypothetical were it not for this new technology. When organoids are infected with the Zika virus, their nerve cells die and the resulting organoids are much smaller than their uninfected counterparts, much like the ones we have grown from our microcephaly patient.

Organoids most likely will help with other Zika research. By growing multiple organoids and infecting each with a separate viral strain from different areas of the world, we can try to understand why the virus causes microcephaly in some regions but not others. We can also use organoids to explore why only some individuals develop microcephaly after Zika exposure. And organoids may be used to identify the docking point, or receptor, used by the virus to gain entry to cells—and they may be critical

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for testing potential anti-Zika drugs before moving them into clinical trials with patients.

A second technique propelling the use of organoids is genome engineering—a collection of methods that allows researchers to alter a cell's genetic code. Organoids engineered to incorporate mutations suspected of causing disease can enable researchers to determine whether the genetic defects actually do lead to illness. Ultimately investigators may be able to evaluate whether repairing those mutations would generate healthy organoids; if so, the work could lead to new treatments that counteract the mutations' effects.

Neuroscientists are eager to explore still other applications of mini-brain technology, such as drug development. The technology can assess whether new medications affect brain tissue in desired ways, obviating the need for animal testing and thus saving on the costs of drug development. The organoids can also let scientists identify unwanted effects on the developing human brain, thereby preventing drugs that would be harmful during gestation from ever reaching a pregnant woman. If the notorious drug thalidomide, which disrupts the developing brain early in pregnancy and causes other birth defects, had been tested in this way, it presumably would not have been prescribed for morning sickness in the late 1950s and 1960s.

Organoids are becoming an invaluable tool for evolutionary biologists. They can be used to identify genes responsible for the enormous size of the human brain compared with other primates. Contrasting human and primate genomes has already identified genes that might be responsible for cognitive functions, such as language, that are unique to humans. Understanding the workings of these genes has remained largely a matter of speculation. Now scientists can introduce genes isolated from monkeys and apes into organoids to determine how they affect brain development. Researchers can also insert genes or entire regions of a genome into a monkey organoid to make them function in a more humanlike manner.

SHOULD WE BE AFRAID?

THE IDEA OF GROWING a human brain in a dish is sure to make some people squeamish. Movies such as *The Matrix* come to mind that evoke fantasies about lab-grown brains developing thoughts or even personalities. These are needless fears. The probability that a lab-grown brain will develop a mind of its own is nil. An organoid is not a "humanoid" in a jar and will not be one even in the far future. Any conscious being needs to be able to process information from the senses to develop an internal mental model of reality. Organoids are neither able to see nor hear and lack any sensory input. Even if we were to connect them to a camera and a microphone, the incoming visual and auditory information would still need to be translated into a form that could be understood by these brain cells in a dish—and, as things stand, providing that translation is an insurmountable technical challenge.

Organoids are not functional brains, only lumps of tissue that imitate the molecular and cellular functioning of the organ at spectacular levels of detail. They are similar to pieces of tissue removed during brain surgery, not conscious beings.

Still, growing an organoid does raise certain ethical and legal issues. All organoids derive from cells taken from individuals who have certain legal rights. As such, performing this work in the lab must conform to the same set of legal and ethical procedures used for samples taken from patients in any industrial country. Patients, of course, must give permission before their cells can be used for research. The same set of rules applies with organoids. But even when the benefits are clearly explained, donors may not at first feel comfortable with the idea of having their cells cultured into brainlike structures.

WHAT'S NEXT?

THE BENEFITS of this cellular technology outweigh any possible downside. Cerebral organoids have laid the foundation for performing realistic medical and toxicology experiments in human tissue, without the need for animal experiments. Even so, I and others would like to improve them. For instance, the current generation lacks blood vessels. That absence is not a problem during the early stages of organoid development, but over time cells start dying from lack of oxygen and nutrients. In theory, it should be possible to provide blood vessels, either through new 3-D-printing techniques or by growing them from stem cells. Blood vessels are known to grow into the brain, a process that could potentially be recapitulated with a 3-D culture.

In another challenge, we want to make organoids that, in common with an actual brain, have front-to-back, top-to-bottom and left-to-right axes. Unlike a real embryo that has clearly defined body axes, organoids lack a front-to-back and head-to-tail axis. As a result, they develop randomly, so that their individual parts have different orientations. In the developing brain, complex signaling systems give a brain its sense of up versus down—and these same chemicals may ultimately do so for organoids as well. Modern biotechnology methods can generate tissue cultures in which the chemicals needed to spur cell growth during development are present. These techniques may eventually result in the formation of organoids with a forebrain on one end and the hindbrain at the opposite end.

We have already begun to push forward to begin to look for ways to overcome these barriers. We have demonstrated technical feats that we could only dream of a few years ago. Organoids are already helping to achieve a better understanding of disease and are assisting in developing drug candidates. The ability to grow parts of a brain and work with the living sample has begun to open an entirely new chapter in biological research by providing vastly more realistic lab cultures—and at times even a reasonable alternative to using animals in doing research. SA

Juergen A. Knoblich is a senior scientist and deputy scientific director of the Institute of Molecular Biotechnology of the Austrian Academy of Sciences in Vienna. He studies neural stem cells and the development of the fruit fly nervous system.

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IS ANYBODY IN THERE?

Communicating with patients who appear to lack consciousness is becoming a reality

By Adrian M. Owen

Photograph by Gerald Slota

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I CAN TRACE MY SEARCH FOR CONSCIOUSNESS IN NONRESPONSIVE PATIENTS TO THE moment in 1997 when I met Kate, a young teacher from Cambridge, England, who had lapsed into a coma after a flulike illness. Within a few weeks Kate's doctors had declared her to be vegetative—meaning that although she had sleep-wake cycles, she lacked conscious awareness. Her eyes would open and close, and she would appear to look fleetingly around the hospital room, but she showed no signs of inner life and no responses to prompting by her family or doctors.

I was developing new brain-scanning methods at the University of Cambridge, and David Menon, my colleague there, who is an expert on acute brain injury, suggested that we put Kate into our positron-emission tomography (PET) scanner to see whether we could detect any signs of cognitive activity in her brain. It was a long shot, but we suspected that some of our new brain-imaging approaches just might work. While Kate was inside the machine, we showed her pictures of her friends and family by flashing them on a computer screen, and we looked for any signs of a response from her brain. The results were extraordinary. Not only did her brain respond to the faces, but the pattern of brain activity was strikingly similar to what we and others had seen when we showed the faces of loved ones to healthy, aware individuals.

What did it mean? Was Kate actually conscious despite her outward appearance, or was this some sort of reflexive response? It would take more than 10 years of research and improved methodology before we would know how to answer such questions.

Finding answers had become increasingly urgent. In recent years improvements in trauma care, roadside medicine and intensive care had led to more people surviving serious brain damage and ending up as Kate had—alive but with no evidence of preserved awareness. Such patients can be found in virtually every city and town with a skilled nursing facility. Determining their care and treatment—how much life support to give, how to weigh family wishes and the patient's advance directives (if they exist)—is a thorny ethical thicket, involving anguish and sometimes lawsuits. Some of these patients go on to recover to an extent, although it is difficult to predict which ones will and how much. Others enter a state of minimal consciousness, demonstrating inconsistent but reproducible signs of awareness [*see box on opposite page*]. And still others remain vegetative, sometimes for the rest of their days—which can last decades. Being able to distinguish among these states can make all the difference in determining what decisions are in a patient's best interests.

IMAGINE PLAYING TENNIS

IN THE YEARS FOLLOWING Kate's scan, our team at Cambridge tried many ways to detect hidden awareness—what we call covert consciousness—in patients who had been declared vegetative. We played speech for them—long streams of spoken prose—and compared the response in their brain to what happened when we played speechlike noises that contained no real language. In a number of cases, we observed brain activity in putatively vegetative patients that looked like that of healthy participants—speech-perception regions of the brain would often respond when we played them speech but did not respond when we played them the speechlike noises. As before, however, we were unsure if the seem-

IN BRIEF

Improved trauma care has led to more people surviving brain injury but ending up in vegetative or minimally conscious states. Researchers are devising imaging techniques to determine which patients retain some awareness or might regain consciousness.

Functional magnetic resonance imaging has revealed, surprisingly, that a portion of patients who are labeled "vegetative" are in fact conscious. Some can answer questions by imagining one activity for "yes" and another for "no."

Investigators are now turning to electroencephalographic technology to try to devise a bedside approach to detecting consciousness. On the more distant horizon are brain-computer interfaces that would enable patients with hidden consciousness to communicate.

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ingly normal brain responses reflected an undetected consciousness or if they were more basic, automatic neural signals, largely independent of any higher-level conscious processing.

I carried out a critical follow-up experiment with Menon, neuroscientist Matt Davis and others at Cambridge. We decided to sedate a group of healthy participants—in this case, a group of anesthesiologists—and expose them to the same combination of speech and nonspeech sounds that we had shown could elicit normal patterns of brain activity in some vegetative patients. Surprisingly, when these healthy subjects were rendered unconscious with the short-acting anesthetic propofol, the speech-perception areas of the brain were activated just as strongly as when the participants were wide awake. This crucial piece of evidence showed us that "normal" brain responses to speech in vegetative patients are not a reliable indicator of covert awareness. It seems that the brain processes speech automatically, even when we are not conscious and aware that we are doing it.

It was time to go back to the drawing board. We had to look at the issue of covert consciousness in a different way. The real question was not how we could activate these patients' brains but rather what kind of activity we would have to observe to be convinced that a patient was conscious. We drew our answer from the classic, clinical assessment of consciousness: response to command. This is the familiar squeeze-my-hand-if-you-can-hear-me test so often depicted in medical dramas on television. Of course, our patients were too injured to produce physical responses to commands, but could they produce a measurable brain response by just thinking about it?

Working with Mélanie Boly, a neurologist then in Steven Laureys's laboratory at the University of Liège in Belgium, we set about measuring brain activity while healthy participants imagined doing various tasks, ranging from singing Christmas carols to walking from room to room in their home to playing a vigorous game of tennis. For many such scenarios, mentally performing the task generates a robust and reliable pattern of brain activity that is similar to actually performing the task.

Using functional magnetic resonance imaging, which, unlike PET, requires no injection of tracer chemicals, we found that two of the best tasks were playing the imaginary game of tennis and mentally walking from room to room in one's home. Indeed, in every healthy participant we scanned, the tennis task elicited strong functional MRI activity in the premotor cortex, a brain region that plays a role in planning movement. On the other hand, mentally touring one's home activated the parietal lobe and a deep-brain region called the parahippocampal gyrus, both of which are involved in representing and navigating spatial locations. Just like the TV doctor who tells the patient to "squeeze my hand if you can hear me," we found we could elicit a reliable response to a command, visible by fMRI, by asking the volunteers to "imagine playing tennis if you can hear me."

To our amazement, the technique worked the very first time we tried it with a seemingly vegetative patient. The young woman in question was involved as a pedestrian in a complex traffic accident and had sustained quite severe traumatic brain injuries. She had remained entirely unresponsive for five months before her fMRI scan, and she fulfilled all internationally agreed criteria for a vegetative-state diagnosis. During the scanning session, we instructed her to perform the two mental-imagery tasks repeatedly and in a given sequence. Remarkably, whenever she was asked to imagine playing tennis, significant brain activity showed up in the premotor cortex, just as in the healthy volunteers we had scanned earlier. And when she was asked to imagine walking through her home, we observed significant activity in the parietal lobe and parahippocampal gyrus, again, like the healthy volunteers. On this basis, we concluded that despite her inability to respond physically to external inputs, the patient was conscious. This finding changed how others treated her, including doctors, nurses and her family. In my experience, discovering that a patient is conscious often spurs others to communicate, visit, reminisce, joke and otherwise improve the quality of that patient's life.

DISORDERS OF CONSCIOUSNESS

Lost in the Gray Zone

Consciousness seems like an all-or-nothing affair—either the lights are on, or they are off. But in fact, it can be present in degrees. Conditions in which it is compromised are known as disorders of consciousness (*listed here*). Most often they stem from trauma to the head or events, such as stroke or cardiac arrest, that result in a loss of oxygen to the brain: outcomes tend to be worse for loss of oxygen than for trauma. Patients may progress or regress from one category to another, except in the case of brain death, from which there is no recovery.

Brain death: All functions of the brain and brain stem have permanently ceased.

Coma: Loss of consciousness is complete; cycles of waking and sleeping disappear, and the eyes remain closed. Coma, which rarely lasts more than two to four weeks, is usually temporary; afterward, patients emerge into consciousness or one of the states below.

Vegetative state: Sleep-wake cycles occur, and the eyes may open spontaneously or in response to stimulation, but the only behaviors displayed tend to be reflexive. *Famous cases:* Terri Schiavo, Karen Ann Quinlan.

Minimally conscious state: Patients may seem vegetative but sometimes show signs of awareness, such as reaching for an object, following a command or responding to their environment. *Famous case:* Terry Wallis, who regained consciousness after 19 years.

Locked-in syndrome: Technically, this state is not a disorder of consciousness, because patients are fully conscious; however, they cannot move and may mistakenly be deemed vegetative or minimally conscious. Many patients do retain the ability to blink and move their eyes. *Famous case:* Jean-Dominique Bauby, who dictated a memoir by blinking his left eye.

PUTTING OUR METHOD TO THE TEST

OVER THE NEXT FEW YEARS we tried this technique with as many patients as we could to test its reliability and to seek ways

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to improve it. By 2010, in another collaboration with Laureys and his group in Liège, we reported in the *New England Journal of Medicine* that of 23 patients who had been diagnosed as vegetative, four (17 percent) were able to generate convincing responses in the fMRI scanner. As part of the study, we explored the possibility of using the imaging tasks to have patients answer yes or no questions. One such patient had suffered a traumatic brain injury five years earlier and had been repeatedly diagnosed as vegetative. While in the fMRI machine, he was told he would be asked a series of simple questions and should reply by imagining playing tennis (for "yes") or imagining moving from room to room in his house (for "no"). Incredibly, using this technique, he was able to successfully convey the answers to five questions about his life. He was able to indicate, for example, that "yes," he had brothers, "no," he did not have sisters, and "yes," his father's name was Alexander. (The name is changed here to protect confidentiality.) He also confirmed the last place he had visited on vacation before his injury. Researchers who interpreted the scans as yes or no did not know the answers to these questions, which were constructed based on input from the family [*see box at right*].

Given the complexity of the tasks used, it was evident that the patient had more going on cognitively than mere awareness of his surroundings. He retained a number of higher-level functions: he could switch, sustain and select his focus of attention, comprehend language and choose appropriate responses, maintain and manipulate information in working memory—for example, keeping the instructions for answering yes or no in mind while processing each new question—and recall events from before his accident. Although this patient could reliably and effectively "communicate" with us from within the scanner, no one was able to establish any form of communication at the bedside. Nevertheless, after the fMRI analysis was done, a thorough retesting using standard techniques led doctors to change his assessment to "minimally conscious"—a reminder that diagnosis can be uncertain and changeable for these patients.

In January 2011 I moved my entire research group to Western University in Ontario to pursue this problem with better resources, a bigger team and generous funding from the Canada Excellence Research Chair program. This move allowed us to expand and refine our investigations to tackle a number of crucial questions, including whether we could use our technique to improve patient care. In the case of one young man who had been diagnosed as vegetative for 12 years, we were able to ask a question that could potentially change his life: "Are you in any pain?" In a dramatic moment that was captured for television by a BBC documentary team, he answered, "No," much to our relief.

Another question was more technical. Could we find a test that did not require an fMRI scanner? Performing fMRI in severely brain-injured patients is enormously challenging. In addition to considerations of cost and scanner availability, the physical stress on patients can be high as they are transferred, usually by ambulance, to a suitably equipped fMRI facility. Some patients are unable to remain still in the scanner, whereas metal implants, including plates and pins, which are common following a serious injury, may rule out fMRI altogether.

Our recent efforts have focused on building a less costly, more portable way of assessing brain activity using electroencephalography. EEG relies on noninvasive electrodes attached to

FINDINGS

Reading Minds

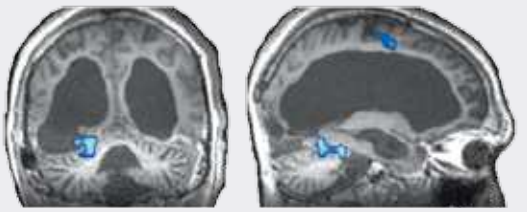
To test a way of detecting consciousness and communicating with unresponsive patients, the author and his colleagues scanned the brain of a man who for five years was thought to be vegetative. They asked him various questions and told him to reply "yes" by imagining playing tennis and "no" by imagining touring his home. Functional MRI scanning of healthy people has shown that the tennis task increases blood flow to motor-planning regions of the brain and that the house tour increases it to spatial regions, making responses easy to distinguish. Remarkably, the man answered five questions correctly, including the two here.

The patient was asked, "Is your father's name Alexander?" He answered "yes" by visualizing himself playing tennis, which lit up a premotor region (*orange* and *yellow*). (The father's name is altered here for confidentiality.) The patient's scan pattern closely matched that of a healthy control subject imagining playing tennis.

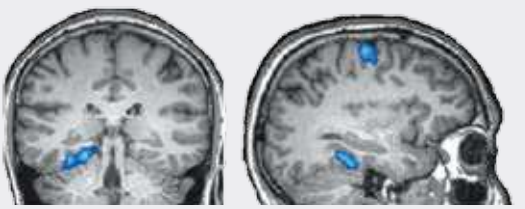
Patient

Control subject

The patient was asked, "Is your father's name Thomas?" He replied "no" by visualizing going from room to room in his home, which lit up spatial regions (*blue*). His scan was strikingly similar to that of the healthy control subject doing the same task.



Patient



Control subject

SOURCE: "WILLFUL MODULATION OF BRAIN ACTIVITY IN DISORDERS OF CONSCIOUSNESS." BY MARTIN M. MONTI ET AL., IN *NEW ENGLAND JOURNAL OF MEDICINE*, VOL. 362, NO. 7; FEBRUARY 18, 2010

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the scalp and measures the activity of groups of neurons in the cortex, the deeply folded outer layers of the brain. It is unaffected by metallic implants and, perhaps most important, can be done at the bedside. Unfortunately, EEG does not easily detect changes in very deep brain structures, and its spatial resolution—its ability to detect a clear response in a particular brain region—is much lower than is the case with fMRI. To deal with these limitations, we adapted our mental-imagery tasks to produce activity on the surface of the cortex, in areas that control simple movements of the arms and legs. Damian Cruse, now at the University of Birmingham in England, found that if he asked healthy participants to imagine clenching their right hand or their toes, he could detect the difference, based on the EEG pattern that was generated. It did not work for everyone, but by 2011 it was reliable enough for us to start testing patients at their bedside.

We bought a Jeep (the "EEJeep"), fitted it with electrodes, amplifiers and the most powerful laptops we could find, and we hit the road, taking our equipment to patients. In November 2011 we reported our findings in the *Lancet*. They were similar to our results with fMRI: three out of 16 (19 percent) of the "vegetative" patients we tested using bedside EEG appeared to be conscious, based on their responses to commands to imagine squeezing their toes or hands. Not everyone was convinced by the study. EEG analysis is notoriously complicated, and the statistical algorithms we used were sufficiently novel and complex that they were challenged by another research group.

Fortunately, we were able to confirm awareness in most of the patients who had responded well in the EEG study by using our more established fMRI technique. More recently, my team has been developing another kind of portable technology known as time-resolved functional near-infrared spectroscopy (fNIRS), which can detect regional brain activity in patients by measuring changes in oxy- and deoxyhemoglobin concentrations in the brain. When participants are asked to imagine playing tennis, the results are comparable to those acquired using fMRI. This new technique can be used at the bedside and is much cheaper than fMRI.

IT IS ALREADY POSSIBLE TO DIRECTLY ASK A PATIENT IF HE OR SHE WANTS TO CONTINUE LIVING IN HIS OR HER CURRENT SITUATION USING OUR FMRI, EEG OR FNIRS TECHNIQUES.

WHAT THE FUTURE HOLDS

WHERE DO WE GO FROM HERE? The notion that we might one day be able to communicate by thought alone has preoccupied scientists and science-fiction writers for decades. The use of fMRI, EEG and fNIRS to detect awareness and begin to communicate with some otherwise nonresponsive patients paves the way for the development of true brain-computer interfaces that would relay a patient's thoughts to the outside world. It seems increasingly likely that such devices, when they become available, will work by translating specific thoughts into yes, no and perhaps other concepts. Creating systems that work for individuals who have sustained major brain injuries will be no easy task, however. Such patients rarely have control over their eye movements, ruling out interfaces that depend on blinking or directing one's gaze, and their depleted cognitive resources—a common result of brain injury—may preclude any system that requires extensive training, as the current ones do.

These obstacles notwithstanding, it seems likely, if not inevitable, that fMRI, EEG, fNIRS and perhaps newer technologies will increasingly be used to detect covert awareness in nonresponsive patients, raising a number of moral and legal questions. In cases where decisions have been made to withdraw nutrition and hydration, it is possible that evidence for covert consciousness could be used to overturn this decision. In principle, it is already possible to directly ask a patient if he or she wants to continue living in his or her current situation using our fMRI, EEG or fNIRS techniques. But would a yes or a no response be enough to signify that the patient has retained the cognitive and emotional capacity to make such an important decision? How many times would the question need to be asked and over how long a period? A 2011 survey of 91 patients with locked-in syndrome—a condition in which consciousness is intact, but the body is paralyzed—suggests that people have a surprising capacity to adapt to extreme disability: most expressed satisfaction with the quality of their lives. Clearly, new ethical and legal frameworks will be needed to guide exactly how such situations are managed and by whom.

As for Kate, a remarkable thing happened. Unlike most of the hundreds of vegetative patients I have seen over the years, she began to recover several months after her scan. She now lives in her own home but still requires round-the-clock assistance. She uses a wheelchair to get around and has learned to speak again. Her cognitive faculties have returned, including her sense of humor and ability to appreciate the profound role that she—and her brain—has played in the process of scientific discovery. Although she did not remember her own brain scan when she first became fully conscious, Kate has since become passionate about the importance of such scans. "It scares me to think of what might have happened if I had not had mine," she wrote in an e-mail to me in 2014. "So please use my case to show people how good they are. I want more people to know about them. It was like magic—it found me." SA

Adrian M. Owen holds the Canada Excellence Research Chair in cognitive neuroscience and imaging at Western University in Ontario. He is author of *Into the Gray Zone: A Neuroscientist Explores the Border between Life and Death* (Scribner, 2017).

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More information on the author's work: www.owenlab.uwo.ca

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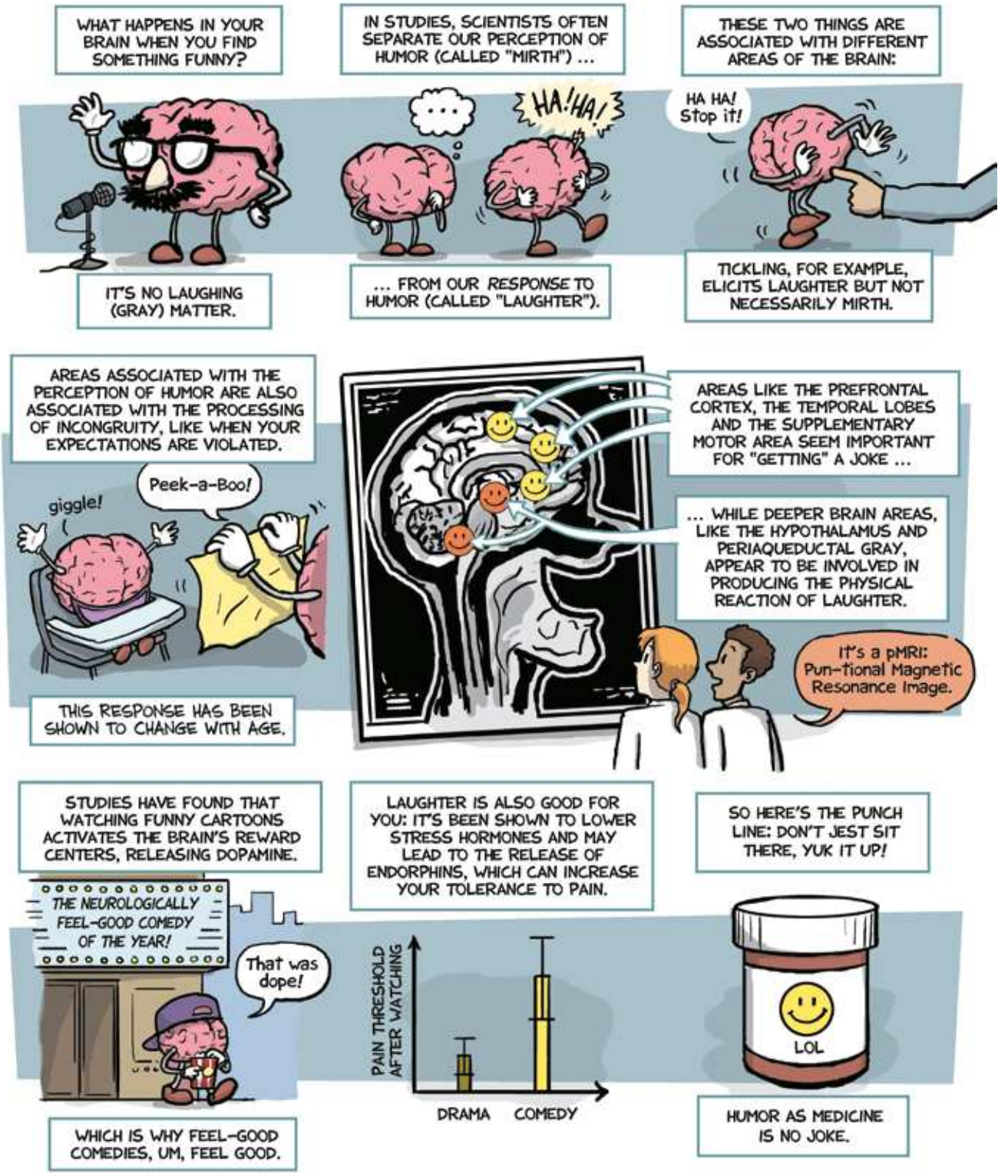
END NOTE

The Brain's Funny Bone

By Dwayne Godwin and Jorge Cham


WHAT HAPPENS IN YOUR BRAIN WHEN YOU FIND SOMETHING FUNNY?
IT'S NO LAUGHING (GRAY) MATTER.
IN STUDIES, SCIENTISTS OFTEN SEPARATE OUR PERCEPTION OF HUMOR (CALLED "MIRTH") ...
HA!HA!
... FROM OUR RESPONSE TO HUMOR (CALLED "LAUGHTER").
THESE TWO THINGS ARE ASSOCIATED WITH DIFFERENT AREAS OF THE BRAIN:
HA HA! Stop it!
TICKLING, FOR EXAMPLE, ELICITS LAUGHTER BUT NOT NECESSARILY MIRTH.
AREAS ASSOCIATED WITH THE PERCEPTION OF HUMOR ARE ALSO ASSOCIATED WITH THE PROCESSING OF INCONGRUITY, LIKE WHEN YOUR EXPECTATIONS ARE VIOLATED.
giggle!
Peek-a-Boo!
THIS RESPONSE HAS BEEN SHOWN TO CHANGE WITH AGE.
AREAS LIKE THE PREFRONTAL CORTEX, THE TEMPORAL LOBES AND THE SUPPLEMENTARY MOTOR AREA SEEM IMPORTANT FOR "GETTING" A JOKE ...
... WHILE DEEPER BRAIN AREAS, LIKE THE HYPOTHALAMUS AND PERIAQUEDUCTAL GRAY, APPEAR TO BE INVOLVED IN PRODUCING THE PHYSICAL REACTION OF LAUGHTER.
It's a pMRI: Pun-tional Magnetic Resonance Image.
STUDIES HAVE FOUND THAT WATCHING FUNNY CARTOONS ACTIVATES THE BRAIN'S REWARD CENTERS, RELEASING DOPAMINE.
THE NEUROLOGICALLY FEEL-GOOD COMEDY OF THE YEAR!
That was dope!
WHICH IS WHY FEEL-GOOD COMEDIES, UM, FEEL GOOD.
LAUGHTER IS ALSO GOOD FOR YOU: IT'S BEEN SHOWN TO LOWER STRESS HORMONES AND MAY LEAD TO THE RELEASE OF ENDORPHINS, WHICH CAN INCREASE YOUR TOLERANCE TO PAIN.
PAIN THRESHOLD AFTER WATCHING
DRAMA
COMEDY
SO HERE'S THE PUNCH LINE: DON'T JEST SIT THERE, YUK IT UP!
LOL
HUMOR AS MEDICINE IS NO JOKE.

Dwayne Godwin is a neuroscientist at the Wake Forest University School of Medicine. **Jorge Cham** draws the comic strip *Piled Higher and Deeper* at www.phdcomics.com

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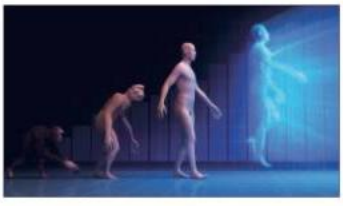

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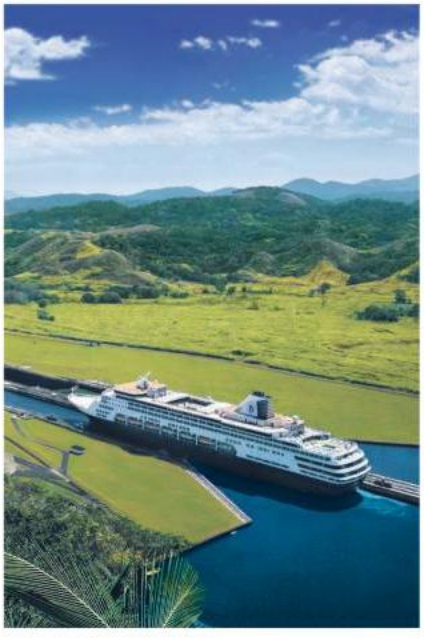

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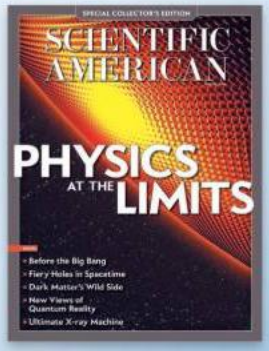

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